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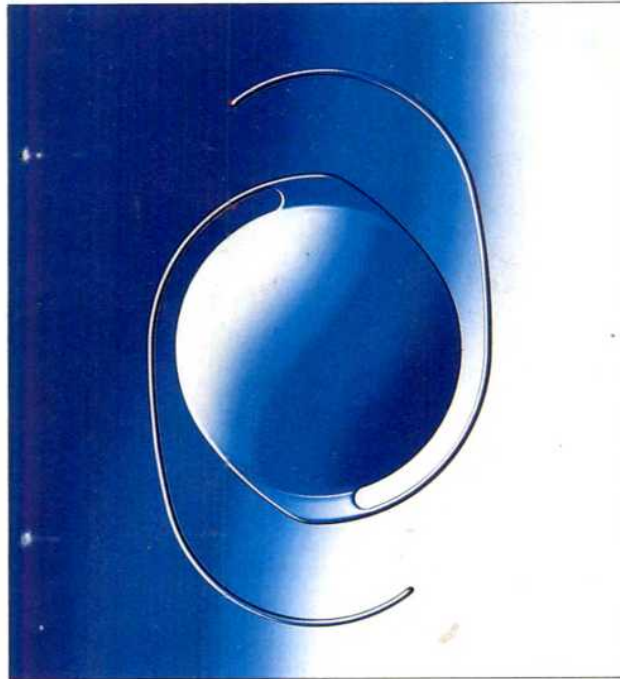
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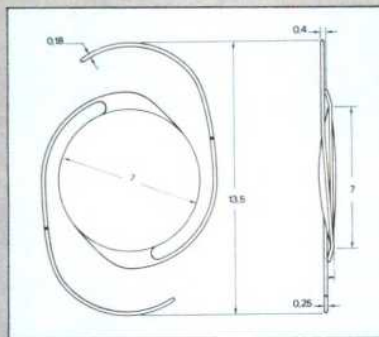


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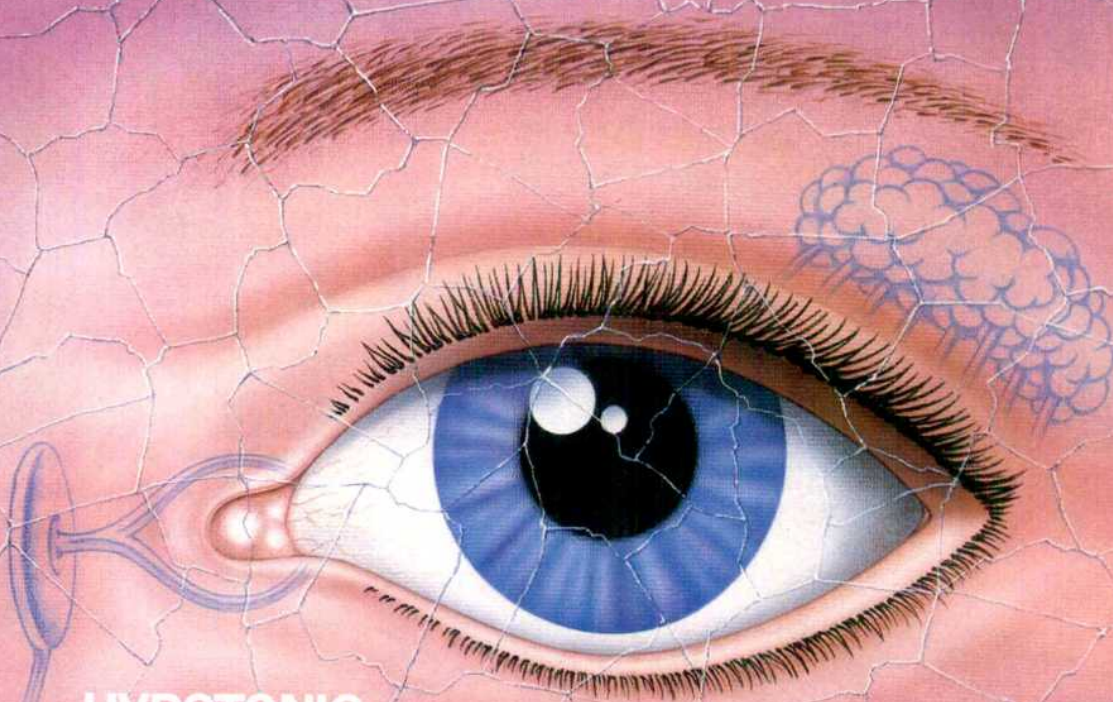
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ALLERGAN PHARMACEUTICALS

SCIENCE WITH VISION

Editorial: Incidence or Prevalence

The methods of conducting the early surveys of glaucoma¹⁻⁴ tended to vary, and few were true population studies. In the Cleveland study,² for example, a large number of persons had their pressures measured on a single 'glaucoma day,' while in Birmingham¹ a sample of 10 000 was aimed at by advertising in newspapers and at places of work. At Bedford³ the subjects were volunteers who did not form a random sample of the population, while at Oxford⁴ subjects were partly patients and relatives attending hospital for non-ocular complaints and partly Services personnel. At Ferndale,¹ however, a determined effort was made to assess the whole population between the ages of 40 and 75 of three villages in the Rhondda Valley, and Stromberg's⁵ survey covered the whole population over the age of 40 years in the Swedish town of Skovde.

Most of the surveys tended to concentrate on tonometry, and indeed some of them were designed to measure only pressure without necessarily looking deeply into the other features of glaucoma. Primary glaucoma was found to occur in from 0.43% of subjects over the age of 40 to 2.9% in the various published studies. This variability probably relates to some extent to sampling methods but more likely to varying diagnostic criteria. For example, Reed and Bendor-Samuel¹ included 17 patients with 'normal' visual fields and six with 'poor co-operation' on field testing but only seven with definite glaucomatous defects in their 30 cases. Their prevalence rate was 2.9%. However, in the Ferndale survey much stricter criteria were employed, and the rate there was only 0.43%.

It has to be remembered that in the 1950s and 1960s routine tonometry was not usually done. Although tonometry is now routine in ordinary ophthalmological examinations, visual field screening is not, though it is likely that careful ophthalmoscopy by a well trained observer is still probably one of the surest methods of detecting glaucoma. But I am wandering off the point I wished to make concerning these early surveys, namely, that they were all, in effect, studies of the prevalence not the incidence of the disease. To those well versed in statistics the two words prevalence and incidence mean different things. I suspect that many clinicians, myself included I regret to have to admit, tend to think of the words as more or less synonymous and do not take much notice of the difference.

This difference is clearly explained in the paper by Bengtsson in the present issue. Prevalence is the

proportion of the population affected at a single point in time, whereas incidence is the proportion becoming affected during a defined period, usually one year. It follows that in self-limiting diseases with a short course annual incidence will probably be greater than prevalence. With an average duration of a year incidence will equal prevalence; while, in diseases that are permanent once contracted, prevalence will depend on the age at which the disease is usually acquired, but will certainly be greater than annual incidence. Bengtsson's study has elements both of a study of prevalence and of incidence. The first survey of the defined population is of necessity one of prevalence. This is followed at intervals of a few years by two further surveys on the same subjects (due allowance being made for the inevitable losses from the original muster), thus enabling the incidence to be determined, since cases detected at the second and third surveys were 'new' cases. The results of this part of the study led to the conclusion that the incidence of manifest glaucoma is 0.24 per annum. Incidentally it should also be noted that the surveys all included routine automatic perimetry, and it was on the perimetric evidence that the diagnosis was firmly based.

It is much more difficult than it might appear at first sight to relate this incidence rate to the sort of prevalence figures we are used to reading about, which as noted above may vary between wide limits averaging perhaps somewhere around 1%. One has to realise that in an extended investigation of this type all sorts of statistical problems arise. Although the same subjects are being studied each time, the composition of each group is quite different because of losses and aging. (The author has done his best to compensate for these difficulties, but it inevitably makes the presentation hard to follow.) Twenty-six cases were found in the intervals between the surveys, giving the average incidence of 0.24% per annum. An average duration of say 10 years would lead to a prevalence rate of 2.4%, which is somewhat on the high side. One has little doubt that the author, whose records seem very detailed, could work out an exact prevalence rate if he wished to, though that is not his primary purpose in presenting this material.

One feels that the chief interest in the paper lies in the final analysis of the total of glaucomatous individuals in the study, combining those from the first prevalence survey (15) (plus three discovered incidentally) with the 26 in the incidence survey, to give a grand total of 44. It is assumed that

the proportions of males and females and the geographical location of cases would be similar in incidence or prevalence surveys, hence the inclusion of the whole 44.

The findings as a result of this are very strange. The female to male ratio is about 2.5-1.0 quite different from findings in all other studies, and the geographical findings are unexpected also, many more cases being found in the 'countryside' than in villages (though 'countryside' is not defined). One is completely baffled by the latter finding, but there is a possibility that the sex distribution could have been influenced by mixing the figures for incidence with those for prevalence. In incidence studies, as explained above, diseases with a short duration are likely to predominate. Now chronic open-angle cases are 'always with us,' whereas successfully treated angle-closure cases are in effect cured, so that angle closure can be considered a disease of short duration. Therefore angle closure will, as was indeed shown in a study in 1958,* figure more prominently in a study of incidence and, because of the sex distribution of angle closure (females outnumber males by 3 to 1) will tend to alter the sex ratio. It is possible, therefore, that some

cases of angle closure might have been included in Bengtsson's study, and this might have contributed to the surprising sex distribution. However, it is most unlikely to be the complete answer and certainly does nothing to explain the geographical peculiarities. Further studies on this population are awaited with interest.

R J H SMITH

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Incidence of manifest glaucoma

BO BENGTSSON

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SUMMARY The incidence of manifest glaucoma was determined by means of repeated automatic perimetry in a defined general population. It was estimated at 0.24% per year. It was largely independent of age but higher in women than in men and higher in the countryside than in the villages. In fact the incidence of manifest glaucoma was five times higher among women in the countryside than among men in the villages.

In a population the occurrence of a disease is described by prevalence and incidence. The proportion being diseased at a certain point of time is called prevalence. The proportion becoming diseased during a certain period is called incidence. In other words: prevalence measures the probability of having a disease; incidence the risk of getting it. Prevalence is the product of the incidence and the duration of a disease. Incidence is, accordingly, the more fundamental of the two concepts.

A single survey of the population suffices to determine the prevalence of a disease. Repeated surveys are needed for a direct measurement of the incidence of asymptomatic cases. Not surprisingly 'the incidence of glaucoma in a defined general population has not been adequately measured'.¹ Existing indirect estimates are far from unanimous.²⁻⁵

We have performed repeated visual field screening^{6,7} during a longitudinal study of the natural history of glaucoma. Very few participants were treated for ocular hypertension. The present material, therefore, provided us with an opportunity to measure the incidence of manifest glaucoma in a defined general population.

Material and methods

Letters within brackets refer to Fig. 1.

All Dalby residents born 1907-21 were listed in December 1976. The list was kept up to date by means of reports on removals and deaths. Of the listed persons 14 were treated for ocular hypertension before the first survey; 1938 were invited and 1511 examined. Manifest glaucoma was diagnosed in 15 persons (V) at the first survey and treatment for

ocular hypertension was started in six others.

During the interval between the first and the second examination 10 subjects left the county and 53 died (B).

Of the 1427 remaining persons 1295 took part in the second survey. Manifest glaucoma was diagnosed in five persons (X). Those not attending were retained in the study (L).

During the interval between the second and the third examination 13 subjects left the county and 160 died (C, CL). Manifest glaucoma was diagnosed in six cases (Y).

Of the 1243 remaining persons 1039 took part in the third survey. All but 32 of them had taken part in the second survey too (PL, ZL).

Age and sex distributions are given in Table 1.

The surveys. Automatic screening perimetry, fundus photography, ophthalmoscopy, slit-lamp examination, and Goldmann tonometry were all attempted in the same way and by the same staff each time on every person who took part in the study. Detailed descriptions of automatic perimetry and optic disc photography, for the present purpose, have been given elsewhere.^{7,8}

Patients followed up for shorter intervals. Patients treated for ocular hypertension were followed up by the author or at the regional hospital. According to the records all had been subjected to automatic perimetry at least once every year. The author used the same methods as in the survey. Patients followed up at the regional hospital were usually subjected to threshold perimetry rather than to screening perimetry.

Definition of manifest glaucoma. A person was considered to suffer from manifest glaucoma when a repeatable visual field defect, consistent with glaucoma and not explicable on other grounds,

Correspondence to Dr B Bengtsson, Vårdcentralen, S-240 10 Dalby, Sweden.

Table 1 Age and sex distribution of the material

Birth year	Removed, died			Did not attend				Acquitted*		With manifest glaucoma							
	B	C	CL	K	L	M	ML	P	PL	T	U	V	W	X	Y	Z	ZL
<i>Men</i>																	
07-11	14	42	2	80	17	21	12	134	3	0	1	2	0	2	0	1	0
12-16	13	33	5	60	25	17	16	189	4	1	1	0	1	1	1	0	0
17-21	15	26	3	82	23	22	12	160	8	0	0	0	0	0	1	1	0
<i>Women</i>																	
07-11	11	24	5	90	25	26	15	149	5	2	0	6	1	1	2	0	0
12-16	7	18	2	52	19	21	11	166	6	0	1	4	0	0	1	2	0
17-21	3	11	2	63	23	16	15	204	5	0	2	3	2	1	1	1	1

B = Removed or died between the first two surveys.

C, CL = Removed or died between the latest two surveys.

K = Did not attend the first survey.

L, CL, ML, PL, ZL = Did not attend the second survey.

M, ML = Did not attend the third survey.

P, PL = Acquitted at the third survey.

T = Detected among persons not attending the first survey.

U = Detected among persons treated for OH before the first survey.

V = Detected among persons examined at the first survey.

W = Detected among persons treated for OH after the first survey.

X = Detected among persons examined at the second survey.

Y = Detected among persons followed after the second survey.

Z, ZL = Detected among persons examined at the third survey.

*Found not to have manifest.

coexisted with a corresponding loss of neural tissue in the optic nerve head of the same eye. Only cases confirmed at a subsequent visit have been included in the present study.

Calculation of incidence. The incidence (I) was calculated as $m/(nF - 0.5 mF)$, where m is the number of cases detected among n persons examined and F the mean interval (in years) between two surveys.

In the calculation of the incidence cases of manifest glaucoma detected before a survey were considered to have been examined and detected at the survey. They were counted only if they still remained in the county at the time of the survey, and their number was reduced through multiplication by the attendance at the survey (attendance=number of persons examined/number invited).

Results

Letters within brackets refer to Fig. 1.

Of the six patients treated for ocular hypertension after the first survey four developed manifest glaucoma before the second survey (W). One patient developed a visual field defect, probably as a result of macular degeneration. The sixth was treated at his own request.

At the second survey we detected five cases of manifest glaucoma (X).

Between the second and the third survey glaucomatous visual field defects were detected in six glaucoma suspects (Y).

At the third survey we detected six cases of manifest glaucoma (Z, ZL).

The mean interval was 2.75 years between the first two surveys and 5.65 years between the two latest ones.

Of 14 patients treated for ocular hypertension from before the start of the first survey two died and five developed manifest glaucoma before the end of the third survey (U). Treatment was discontinued in two of the remaining patients and reduced to a single drop each day in another one.

Among persons not attending the first survey a few were later examined by the author. In this way manifest glaucoma was detected in three additional cases (T). As in the 15 cases detected at the first survey (V) the duration of the visual field defects was of course unknown. It could, however, be roughly estimated from the size of the defects. By this method seven defects were found to be fresh and 11 to be of some duration.

Among surveyed persons the incidence of manifest glaucoma was 0.0024/year between the two first surveys and 0.0019/year between the two latest surveys.

The overall incidence, including that in all persons treated for ocular hypertension was 0.0024/year (SE 0.0005).

This estimate was based on 26 incident cases—that is, all cases of manifest glaucoma known to have appeared after the first survey. The following statements are based on 44 cases—that is, all cases of

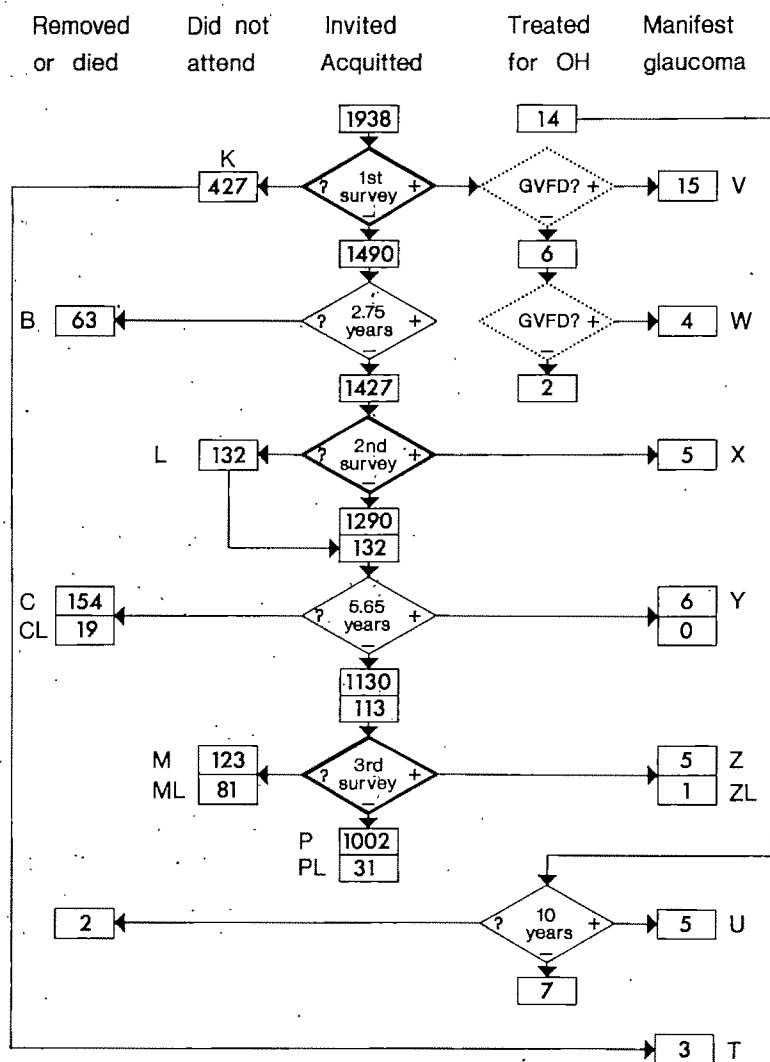


Fig. 1 Flow diagram showing number of persons examined, lost, treated, etc. 'Acquitted' means found not to have manifest glaucoma and not to need treatment for ocular hypertension.

manifest glaucoma detected in 1977-87 in persons born in 1907-21 and living in the Dalby district when listed in December 1976.

Manifest glaucoma was rare in men aged less than 65 years (Fig. 2). With this exception the incidence of glaucoma was largely independent of age (Fig. 2).

Men were as frequent as women in the population, but we found 31 women and only 13 men with manifest glaucoma ($p < 0.01$).

The number of persons living in the countryside when listed before the first survey was only half the number of persons living in the small villages. Nevertheless we found manifest glaucoma in 23 countrymen and 21 villagers ($p < 0.05$).

The age and sex distribution was very nearly the same in the countryside as in the villages, and the

incidence of manifest glaucoma was five times higher among women in the countryside than among men in the villages.

Discussion

The present estimate of the incidence of manifest glaucoma in persons born in 1907-21 (0.24% per year) is similar to that in Dalby residents born before 1907 (0.22% per year),³ but in the case of persons in their 50s and 60s much higher than those obtained elsewhere.^{4,5} It is therefore not surprising that our observation that manifest glaucoma is commoner in women than in men aged under 65^{2,9} has not been confirmed by others.

As so often before,¹⁰ treatment of ocular hyperten-

LEXIS diagram

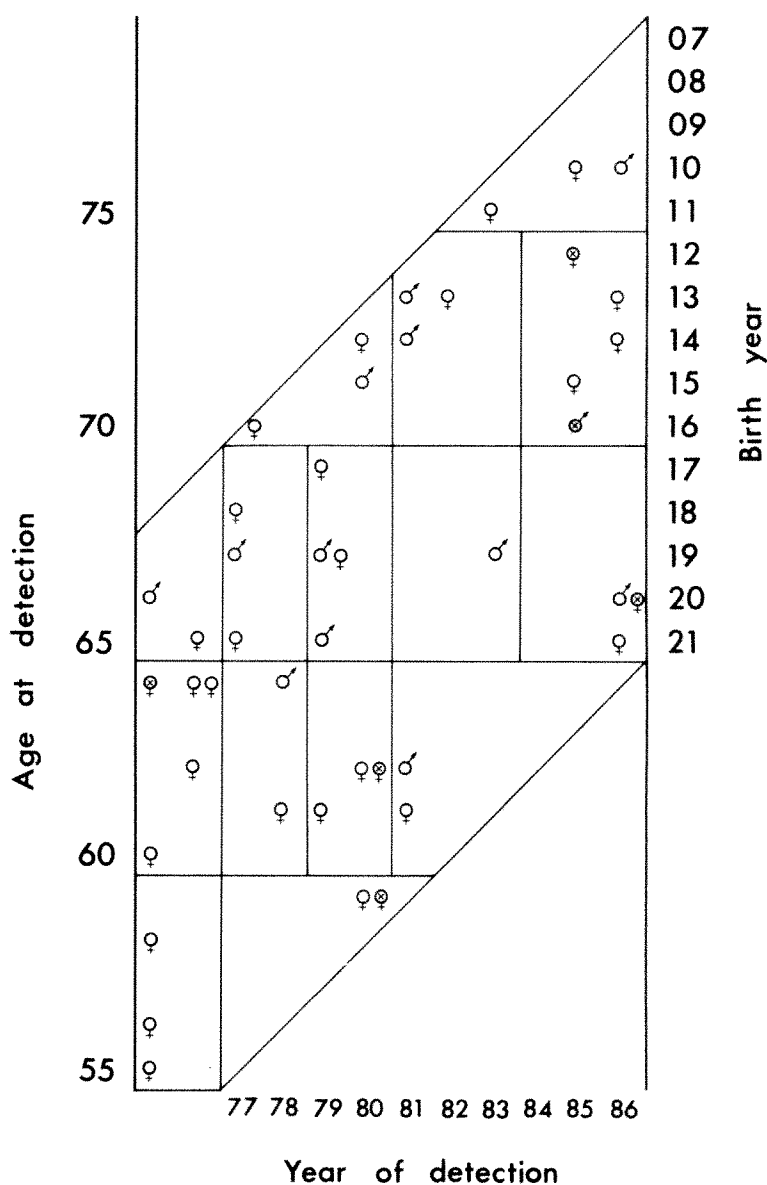


Fig. 2 A Lexis diagram. It describes the incidence of manifest glaucoma in the whole study on the assumption that 11 large defects could have been found at least two years before their actual detection. The total area was divided into 15 compartments, each representing about 1250 person-years. Symbols with X in them represent patients with capsular glaucoma.

sion was found not to prevent the development of glaucomatous visual field defects. To the extent that secondary prevention—that is, early diagnosis and treatment—of glaucoma loses prestige with the profession, primary prevention seems more urgent. The dependence suggested here of the occurrence of manifest glaucoma on residential factors calls for further studies of external causes of glaucoma.

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Simultaneous spontaneous and primary surgical repair of eyelids

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SUMMARY Fifteen patients with suspected malignant lesions of the lower eyelids or inner canthal region, needing large excisions, were managed as day cases with spontaneous repair and simultaneous subtotal primary surgical reconstruction under local anaesthesia. For lesions confined to the lower eyelid, only those patients requiring full-thickness margin-inclusive (FTMI) excisions of more than half the horizontal extent of the eyelid are included in this study – the largest excision being 21×6 mm. For malignant lesions of the inner canthus, only those patients needing moderate to large excision of inner canthal skin and orbicularis with simultaneous FTMI excision of the medial one-third (8×5 mm) of the upper as well as the lower eyelid are included. The 16th patient had traumatic loss of inner canthal tissue. The final cosmetic and functional results in all 16 patients were satisfactory and comparable with the results of competent and in-toto primary surgical reconstructions. For large excisions at the inner canthus spontaneous with partial primary surgical repair allows the use of a less extensive and less elaborate surgical procedure that is within the capabilities of most ophthalmic surgeons.

The potential of the lower and upper eyelids individually—each on its own—to yield a nearly normal functional and cosmetic result solely by spontaneous repair after a moderate sized full-thickness margin-inclusive (FTMI) excision has been established.^{1,2} Before that it had long been known that a competent primary and in-toto surgical reconstruction after such FTMI excisions also produces near normal results. So far the combined management by primary surgical reconstruction of part of the excised area and simultaneous spontaneous repair of the residual defect has not been reported. This study demonstrates the results of such combined management after moderate to large FTMI excisions of the lower eyelid, and large deep excisions of inner canthal skin and orbicularis with contiguous FTMI excisions of medial one-third of the upper as well as the lower eyelids.

Patients and methods

Fifteen consecutive patients with suspected malignant tumours involving the lower eyelid margin, or inner canthal skin, and needing excisions

of 13 mm or more (that is, larger than $\frac{1}{2}$ the horizontal extent of an eyelid) underwent combined treatment with spontaneous repair and simultaneous partial surgical reconstruction under local anaesthesia as day cases. One other patient involved in a traffic accident had general anaesthesia. The ages of these 16 patients ranged between 43 and 88 years, with five patients aged between 43 and 60, seven between 61 and 80, and four between 81 and 88. Their average age was 69 years. The average follow-up period was 17 months, ranging between 6 months and 3.8 years.

These 16 patients can be subdivided into three groups: *Group 1: Full-thickness margin-inclusive (FTMI) excision of lower eyelid.* Five patient had FTMI excision of more than half the horizontal and 6 mm of vertical extent of the lower eyelid. The smallest excision was 13×7 mm and the largest was 21×6 mm. These FTMI defects underwent *partial* surgical reconstruction by one of the following three methods:

(i) For very large FTMI excision of the lower lid, *subtotal* full-thickness surgical reconstruction of only the central area of the defect was carried out in two layers—posterior lamellar and cutaneous—with a tarsoconjunctival sliding flap from the ipsilateral

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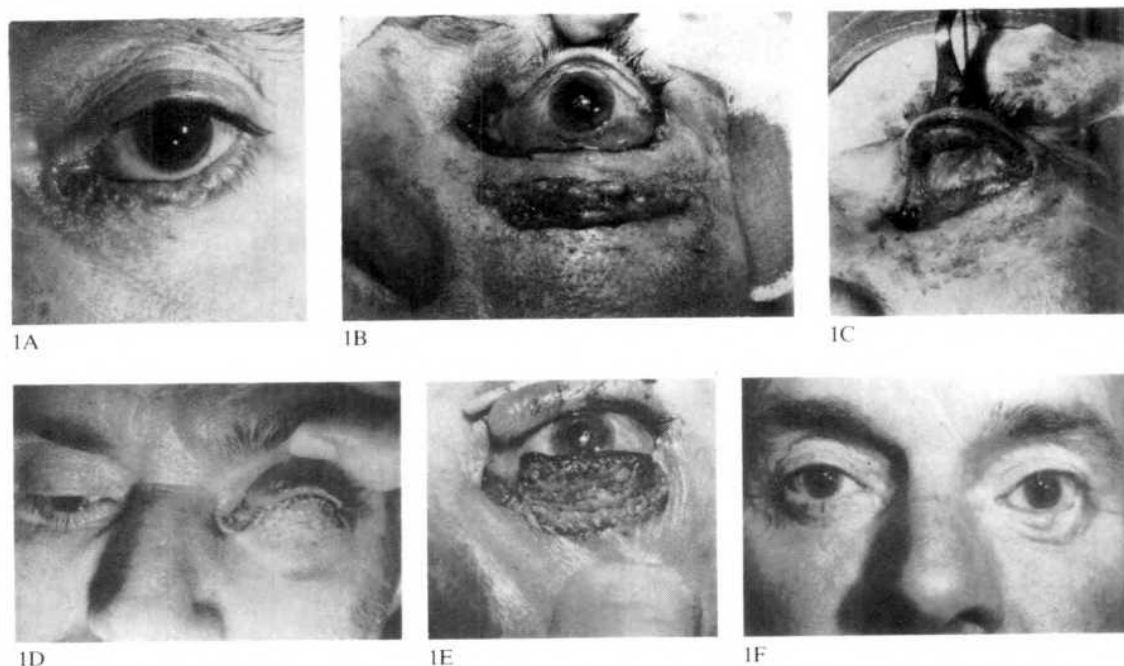


Fig. 1 (A) Rodent ulcer of 7 years' duration, involving medial two-thirds of left lower eyelid margin and palpebral conjunctiva in a Caucasian male aged 64, treated under local anaesthesia as a day case. (B) FTMI excision of 26×6 mm (including 5 mm of inner canthal skin), with 4×5 mm FTMI excision of upper eyelid. The extent of excision is shown by the area xabcfg in Fig. 2. (C, D) The central cross hatched area dehk (Fig. 2) of 13×6 mm was repaired in full thickness with a tarsal strip and Müller's muscle flap and a full-thickness postauricular skin graft. The remaining defects xabcdk and efgh (Fig. 2) were allowed to heal by spontaneous repair. (E) Appearance at one week. (F) Final appearance at 3 months. Note the author's modification of Desmarres' retractor in Fig. C.

upper eyelid, and a full-thickness skin graft (FTSG) to cover the sliding tarsal conjunctival flap. About 3 mm of the FTMI defect on either side of this centrally reconstructed defect was allowed to heal by spontaneous repair. For the patient depicted in Fig. 1A–F a large FTMI excision of 26×6 mm was carried out. Of this large defect only the central area of 13×6 mm was reconstructed in full-thickness (that is, in two layers) with a tarsal conjunctival sliding flap from the ipsilateral upper eyelid. The sliding flap included a 3 mm tarsal strip and Müller's muscle. This flap was sutured to the horizontal edge of the remnant of the palpebral conjunctiva of the lower lid. The anterior lamella was reconstructed with a 13×6 mm full-thickness skin graft tethered with marginal and central sutures. The remaining FTMI defects xabcdk and efgh (Fig. 2) were allowed to undergo spontaneous repair. The tarsal conjunctival flap was severed on the 7th day. In retrospect this division should have been postponed for at least three more weeks to avoid the formation of the small notch at the junction of the lateral quarter of the lower lid.

(ii) For moderate to large (13 – 18×6 mm) FTMI defects of the lower eyelid only the posterior lamellar

defect was repaired with a tarsal conjunctival flap from the ipsilateral upper eyelid. The anterior lamellar defect superficial to the tarsal conjunctival flap was allowed to heal by spontaneous repair. The horizontal extent of the tarsal conjunctival flap was 6 mm less than that of the FTMI excision, as it is usually possible to pull together the sides of FTMI defects by a quarter (that is, 6 mm) of the full width of an eyelid. Therefore the entire posterior lamella was made good without leaving any defect of the posterior lamella. The anterior lamella was not reconstructed with an FTSG, but was allowed to heal spontaneously. The tarsal conjunctival flap was sutured to the three sides of the posterior lamellar defect and was divided, under local anaesthesia, as a day case, at a second stage in about three weeks. (Fig. 3A–F).

(iii) In two patients the tumour did not involve the lid margin but came to within 3 mm of the margin. In these cases an asymmetrical FTMI excision was carried out. The cutaneous lamellar excision extended 8 mm downwards from the lid margin and 13 mm horizontally. The posterior lamellar excision was 3 mm in height from the lid margin and a full

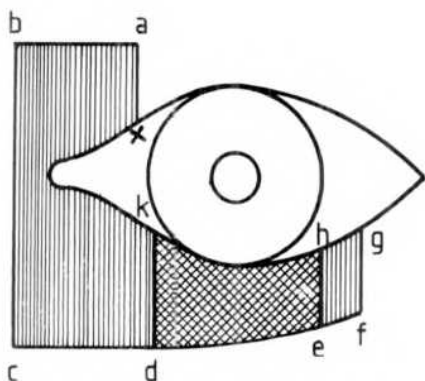


Fig. 2 Diagrammatic representation to simplify descriptions of the surgical procedure for Fig. 1. Vertically striped areas xabcdk and efgh were allowed to heal by spontaneous repair.

13 mm in horizontal extent. Therefore the FTMI excision was 13×3 mm, the remaining excision being of the anterior lamella. In these patients, only the entire anterior lamellar defect was made good with skin graft (FTSG) of 13×8 mm and the entire posterior lamellar defect of 13×3 mm was allowed to heal by spontaneous repair (Fig. 4A–D).

Group 2: Large excision of inner canthal skin and orbicularis with simultaneous contiguous FTMI excisions of medial one-third of the upper as well as the

lower eyelid. In 10 patients in this group such wide excision was mandatory because the rodent ulcers were in threatening proximity to the upper and lower eyelids. The average excision in this group was 30×25 mm, including the FTMI excisions of the upper and lower eyelids. The inner canthal skin and orbicularis defect was made good with a skin graft (FTSG) by tethering the skin graft to the periosteum with central and marginal sutures by the author's technique, described previously.¹⁴ The FTMI defects of the medial one-third (8×5 mm) each of the upper and lower eyelid were allowed to heal by spontaneous repair (Figs. 5, 6A–E).

Group 3: Traumatic lacerations with loss of inner canthal tissue. There was only one patient in this 'group'. She had severe bony injuries of limbs, FTMI lacerations of left upper eyelid, caruncle, plica, and severance of the medial canthal tendon, as well as loss of an irregular patch of skin and orbicularis about 10 mm in diameter overlying the lacrimal sac. Primary surgical repair only of the FTMI laceration of the upper eyelid was carried out. The remaining peripalpebral wounds were allowed to heal by spontaneous repair.

SURGICAL TECHNIQUE AND MANAGEMENT

The 15 patients with eyelid tumours were treated as day cases. The excision and partial surgical recon-

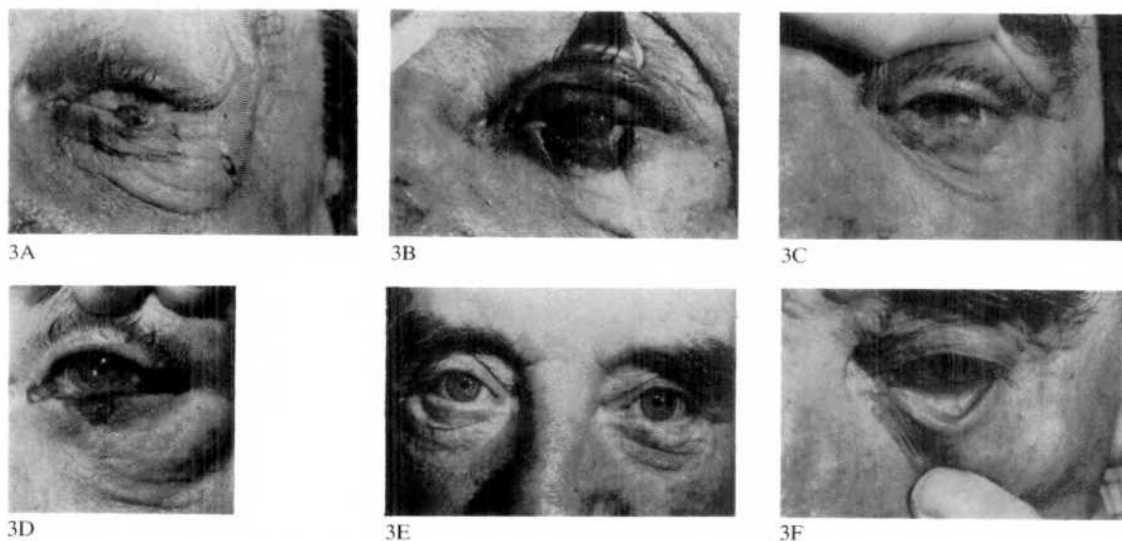


Fig. 3 (A) Rodent ulcer of left lower eyelid margin in a Caucasian male aged 65. (B) FTMI excision 13×7 mm. Ipsilateral upper eyelid is shown everted to obtain a tarsconjunctival sliding flap of 8 mm in horizontal extent and including 8×3 mm tarsal strip with attached Müller's muscle. The sides of the FTMI excision of 13 mm were pulled together by about 6 mm to suture the 8 mm wide tarsconjunctival flap to the remnant of the lower lid conjunctiva on the three sides. The anterior lamellar defect was allowed to heal by spontaneous repair. (C) Appearance of the tarsconjunctival flap on the seventh postoperative day. (D) Appearance at three weeks, immediately after the severance of the tarsconjunctival flap. The anterior lamellar defect has healed by nearly 75%. (E, F) Final appearance at three months.

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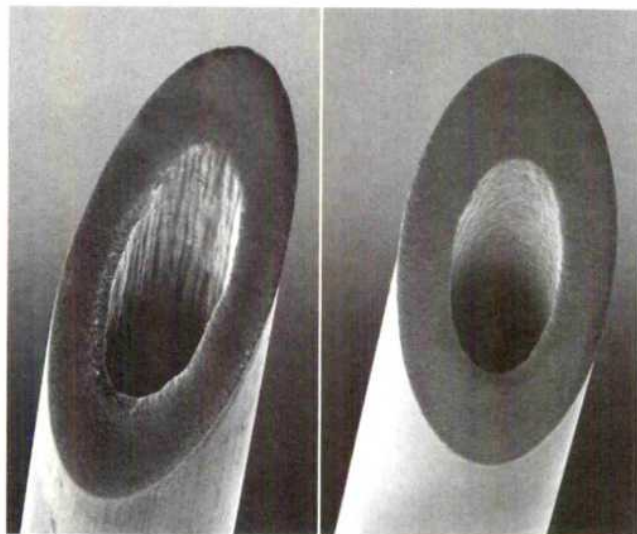
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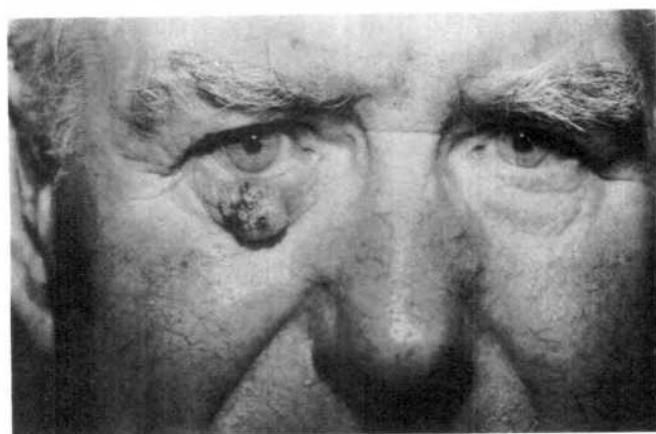
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Fig. 4 (A) Keratoacanthoma of 'two years' duration, affecting the right lower eyelid of a Caucasian male aged 71. The excision was asymmetrical in that the cutaneous lamellar excision extended 8 mm downwards from the lid margin and was 13 mm in horizontal extent. The posterior lamellar excision was 3 mm in height and 13 mm horizontally. The FTMI defect was therefore 13×3 mm. (B) The entire anterior lamellar defect was restructured with a 13×8 mm FTSG, while the posterior lamellar defect was allowed to heal by spontaneous repair. (C, D) Final result at three months.

struction was carried out under local anaesthesia with lignocaine 2% and bupivacaine 0.5% (Marcain) with adrenaline. The patient with traumatic laceration had numerous bony injuries for which she had general anaesthesia. The partial surgical repair of her palpebral and surrounding injuries was carried out at the same time. The details of surgical procedures in the remaining patients have been given above and with the captions of Figs. 1 to 6.

At the end of the partial surgical reconstruction antibiotic eye ointment was instilled and a Cartella shield was applied as the sole dressing. All patients were given 2 tablets of cotrimoxazole (Septrin) twice daily for 5 days and antibiotic eye ointment to be applied twice daily to the eyelids, the skin graft, and

its donor site. The patients were seen for the first dressing at 48 hours, and on the seventh postoperative day for removal of sutures. Thereafter the follow-up period was progressively increased to attain six-monthly follow-up.

Results

The functional and cosmetic results were as normal and satisfactory as the published results of total surgical reconstructions of similar defects implemented by various competent oculoplastic surgeons.^{6,9} There were no palpebral or ocular complications in any patient either during convalescence or subsequently. In four patients a

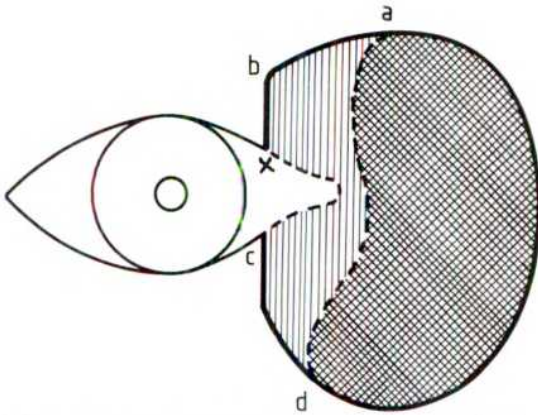


Fig. 5 Diagrammatic representation of Fig. 6. Area abxcd was allowed to heal by spontaneous repair and included 6×5 mm FTMI defect each of the upper and lower eyelid. The reniform cross hatched area was reconstructed with skin graft (FTSG).

planned second stage minor procedure for severance of the tarsoconjunctival flap from the upper eyelid was carried out under local anaesthesia as day cases, between one and three weeks after the initial surgery. The single patient in group 3, with traumatic loss of inner canthal skin, developed a pseudoepicanthic

fold which improved to almost normal in about six months. She also needed minor secondary surgery to correct the stenosed everted left lower lacrimal punctum. A one-snip dilatation of the punctum and its repositioning by excision of an ellipse of palpebral conjunctiva of the lower eyelid at the inner canthus was carried out nearly a year after the initial injury. Of suspected rodent ulcers in the 15 patients histology confirmed the clinical diagnosis in 14. Keratoacanthoma was reported in the remaining patient. In all the 15 patients complete excision with good histological clearance was reported. There has been no recurrence of tumour in any of these 15 patients.

Discussion

The current teaching of oculoplastic surgery is based on the assumption that defects created by excision of palpebral or peripalpebral lesions *must* be repaired immediately by total primary surgical reconstruction. Traditionally, FTMI defects of lower eyelids are reconstituted in two layers—tarsoconjunctival and cutaneous—at least one of which should be a flap with its blood supply intact. The second layer can then be a free graft from a remote or adjacent donor site.¹⁰⁻¹² Large defects at either canthus are usually

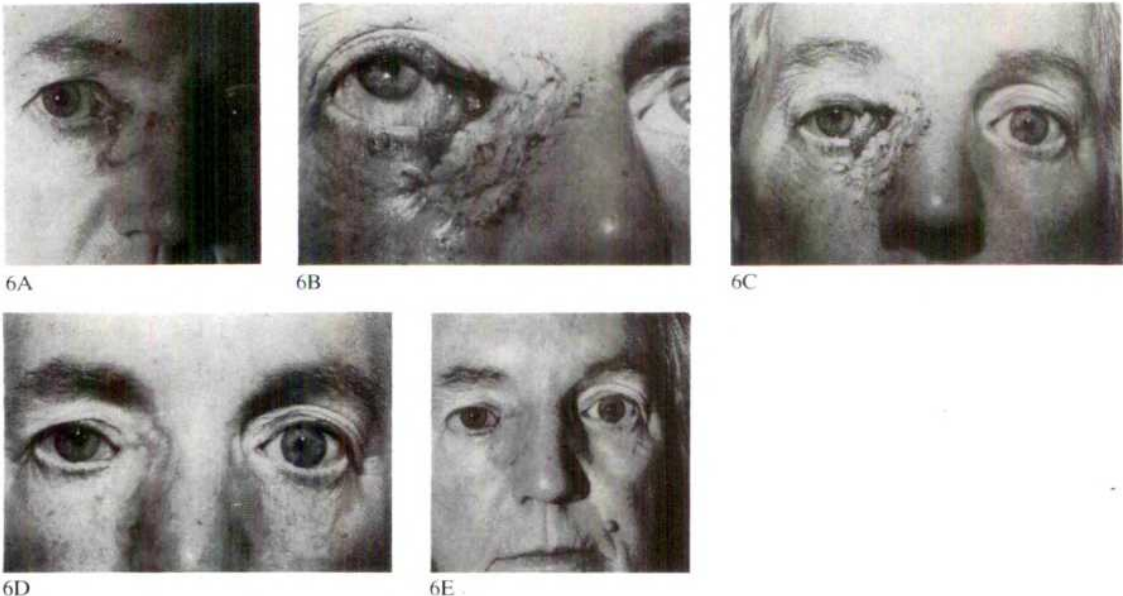


Fig. 6 (A) Multicentric rodent ulcer at inner canthus of a Caucasian female aged 65. The extent of the excision was 30 mm in diameter and included FTMI excision of 6×5 mm of upper lid and 6×6 mm of the lower lid. Surgery under local anaesthesia as a day case included skin graft (FTSG) from inner arm sutured with the author's technique of central and marginal sutures, in the cross hatched area of Fig. 5. The FTMI defects (depicted by vertical striped area abxcd in Fig. 5) and the residual defect of the adjoining inner canthal area, were allowed to heal by spontaneous repair. (B, C) Healthy appearance on first dressing at 48 hours. (D, E) Final appearance at three months and at 18 months.

repaired with a skin flap from near by.⁵⁻⁸ There are no reports so far of exploiting the combined management of spontaneous repair simultaneously with primary surgical reconstruction. Therefore, in addition to being the first report of such combined management, this study highlights the following points: (1) Such combined management gives satisfactory cosmetic and functional results. (2) Simultaneous FTMI defects of ipsilateral upper and lower eyelids (8×5 mm each) heal as effectively and normally as does a similar FTMI defect of each eyelid individually as already reported.^{1,2} (3) As a consequence of this, large defects at the inner canthus can be treated simply with a skin graft (FTSG) under local anaesthesia on a day basis, with the FTMI defects of both eyelids being allowed to reform by spontaneous repair. (4) With lesions confined only to the lower eyelid large FTMI defects yield satisfactory results from the various methods of subtotal full-thickness or full-width lamellar surgical reconstruction in conjunction with spontaneous repair of the residual defect.

The most crucial point to emerge from this study is that large excisions at the inner canthus with simultaneous FTMI excision of adjacent one-third of upper and lower eyelids need a less extensive, simple surgical reconstruction with a skin graft (FTSG), which if secured with the central suturing technique described by the author^{4,12} allows consistently good results. These central sutures act as a combined pressing and immobilising agent and thereby prevent haematoma formation under the graft. The patients can therefore be treated as day cases, without any restrictions on their postoperative activity.

It is not possible to obtain such large skin grafts from the postauricular region, but the supraclavicular region is an excellent donor site that provides good colour match. The conventional method of surgical repair of large defects at the inner canthus is by a rotational skin flap from the forehead. The main disadvantage of such a flap is the distortion and scarring produced on a readily visible part of the face. Moreover, such a flap does not necessarily provide a good colour match as seen in some postoperative results.¹³⁻¹⁵ It therefore has no advantage over a large skin graft (FTSG), especially if the graft is obtained from the supraclavicular region, where the skin is hairless and provides a satisfactory colour match. In addition to the reconstruction of the skin defect at the inner canthus conventional surgical management would have entailed full-thickness reconstruction in mucosal and cutaneous layers of any coexisting FTMI defect of the eyelids. Such reconstructions are difficult and complex procedures that demand the skill of a specialist oculoplastic surgeon, whereas, the combined spontaneous and partial surgical repair

shown here (Figs. 5, 6) can be carried out by an ophthalmic surgeon with an interest in plastic surgery.

The combined management does not confer any worthwhile advantage in the management of moderate or large FTMI excisions confined only to the lower eyelid, because any surgeon capable of instituting a 12 mm wide tarsoconjunctival sliding flap from the upper eyelid could almost as readily obtain an 18 mm wide flap and a skin graft (FTSG) to reconstruct the entire defect. The same applies to full-width but lamellar reconstructions. However, for these large FTMI defects confined to the lower lid, the study documents the feasibility and the scope of spontaneous repair if only for its scientific interest. By conventional criteria all 16 patients in this study would have been treated by primary and solely surgical reconstruction in toto to achieve similar results.

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Functional lid surgery in Down's syndrome

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SUMMARY Down's syndrome is associated with characteristic eyelid abnormalities. Ten patients presented with lid abnormalities leading to corneal problems. Five patients had ectropion, four of whom required skin grafting to correct the abnormality. One patient had entropion and four had chronic blepharoconjunctivitis leading to trichiasis, which was treated with double freeze thaw cryotherapy.

Down's syndrome is associated with a wide variety of anatomical and biochemical abnormalities including congenital mental retardation, congenital heart defects, immune-system deficiencies, and ocular abnormalities—most commonly cataracts, keratoconus, Brushfield spots, and strabismus. The incidence of the disease is approximately 1 in 700 live births and becomes greater with increasing parental age.¹ The characteristic facial features associated with Down's syndrome include macroglossia, hypotonia of the lower lip, receding chin, hypoplasia of the nasal bridge, epicanthic folds, oblique lid axis, and dysplastic ears. In 1977 Hohler described a case of a girl with Down's syndrome in whom he undertook facial plastic surgery purely for cosmesis,² and since then there have been other reports describing the results of cosmetic facial plastic surgery for Down's syndrome.^{3,4} In some cases however, the characteristic lid abnormalities may require correction for functional reasons. In particular, ectropion due to skin shortage may lead to corneal exposure, and trichiasis resulting from chronic blepharitis may similarly lead to corneal problems.

We report on 10 patients who presented with lid abnormalities leading to corneal problems, nine of whom underwent lid surgery.

Patients and methods

Fifty four patients with Down's syndrome who had attended the hospital were studied; of these 10 had eyelid problems directly related to their disease, and the rest had other congenital ocular abnormalities. There were five male and five female patients. The age range at presentation was 7 months to 55 years.

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ECTROPION GROUP (FIVE PATIENTS)

Four patients had bilateral upper and lower lid ectropion as a result of severe lid skin shortage (Fig. 1), and two developed spontaneous eversion of the lids during sleep and on crying (Fig. 2). All had poor lid closure, with an inadequate blink response and signs of bilateral corneal exposure in the interpalpebral zone. Three patients, all of whom had had previous bilateral tarsorrhaphies which had broken down and failed to provide adequate corneal protection, developed permanent corneal scarring in the interpalpebral zone (Fig. 3); one of these had developed a corneal abscess. The ectropion was treated in all cases with full thickness skin grafting to correct the skin shortage, postauricular skin being used as the donor site (Fig. 4). In three patients all four lids were grafted and in the other patient postauricular Wolf grafts to the upper lids were combined with recession of the levator palpebrae superioris. Although there was skin shortage of the lower lids, it was not considered severe enough to warrant surgery. Four years later this patient required further surgery as result of corneal exposure. Consequently bilateral lower lid scleral grafts and skin grafts from the upper arm, together with bilateral



Fig. 1 Child with upper and lower lid ectropion.



Fig. 2 Spontaneous eversion of the lids on crying.

lower lid shortening for excess lid laxity, were performed. In another patient lid skin grafting was combined with division of tarsorrhaphies and horizontal shortening of the lower lids (Fig. 5).

The fifth patient with ectropion in this group was a 55-year-old man. He had bilateral lower lid ectropion, bilateral blepharitis, madarosis, and corneal scarring in the interpalpebral area. However, the lid abnormalities were not considered severe enough to warrant surgery, and he was treated with ocular lubricants alone.

ENTROPION GROUP (ONE PATIENT)

An 11-year-old girl presented with epiphora. On examination she had bilateral upper and lower lid entropion more marked medially, with punctate staining of both corneas. The entropion was corrected surgically with an anterior lamellar repositioning of the upper lids and plication of the lower lid retractors (Jones type procedure).

TRICHIASIS GROUP (FOUR PATIENTS)

Four adult patients had trichiasis leading to surface corneal changes, but not associated with any malposition of the lid. Their ages were 15, 22, 27, and 54 years. In each case the trichiasis was associated with severe chronic blepharitis, and a variety of organisms were identified from lid margin cultures, including *Staphylococcus epidermidis* (three patients), *Haemophilus influenzae* (one patient), and *Corynebacterium xerosis* and a haemolytic strepto-



Fig. 3 Patient with upper and lower lid ectropion, bilateral tarsorrhaphies, and corneal scarring.

coccus (one patient). One of this group had been referred for corneal grafting for keratoconus but had been found to have trichiasis and lash ptosis which needed correction prior to corneal surgery. The trichiasis in these patients was treated with double freeze thaw cryotherapy to the lid margin. The lid was frozen from the lid surface with a special probe to a temperature of -20°C ; the tissues were then allowed to thaw spontaneously and the freeze thaw cycle was repeated. The temperature was monitored with a thermocouple needle placed deep to orbicularis oculi and superficial to the tarsal plate in the region of the lash follicles. One patient had electrolysis to two isolated lashes on the right upper lid in addition to cryotherapy of the other lids.

Results

Ectropion group. In the four patients who underwent full thickness skin grafting the surgery corrected the ectropion as well as enabling good lid closure and improved corneal protection (Fig. 4). In all these cases the signs of corneal exposure resolved, though in three patients there was residual corneal scarring (Fig. 5). The cosmetic results of skin grafting in these young children were not good but improved with time. One patient in this group with ectropion, a 55-year-old man, did not require surgery but responded well to treatment with ocular lubricants alone.



Fig. 4 Same patient as in Fig. 1 postoperatively.



Fig. 5 Same patient as in Figs. 2 and 3 postoperatively.

Entropion group. Surgery corrected both upper and lower lid entropion in this case.

Trichiasis group. Cryotherapy was effective in controlling the trichiasis in all four patients with no recurrences. The patient with keratoconus subsequently underwent successful bilateral penetrating keratoplasty.

Discussion

Congenital ectropion is a well recognised and potentially sight threatening condition seen in children with Down's syndrome but rarely other children. Many cases respond to conservative treatment alone,⁷ but in children with Down's syndrome surgical correction is often necessary.^{8,9} In this study four of our fifty-four patients had congenital ectropion leading to corneal exposure and requiring surgery. Two cases were severe enough to lead to spontaneous eversion of the lids, which increased on forced lid closure. In three patients lagophthalmos and associated corneal exposure led to corneal ulceration and permanent scarring; in one case it was severe enough to lead to a corneal abscess and hypopyon. It is therefore imperative that cases with significant corneal exposure are treated promptly with appropriate surgical techniques to prevent any permanent corneal complications.

In these patients the mechanism for the ectropion was skin shortage of the lids leading to vertical shortening of the anterior lid lamella, which pulls the lid margin away from the globe and results in ectropion. Associated conjunctival inflammation and chemosis further aggravate the condition, and in long-standing cases the problem may be compounded by the development of horizontal lid laxity.

Lateral tarsorrhaphies and horizontal lid shortening procedures have been used in an attempt to improve corneal cover but with variable results.^{8,9} Three of our patients had had previous tarsorrhaphies which had broken down, resulting in poor corneal protection, with one patient developing a corneal abscess and hypopyon as a result of corneal exposure. This technique should not be used in young children in whom the primary abnormality is skin shortage but reserved for cases of paralytic ectropion requiring temporary corneal protection.

We believe that the correct management of the congenital ectropion in these cases is correction of the underlying skin shortage with skin grafting. In most cases there is skin shortage of both upper and lower lids, and therefore transposition flaps cannot be used. Full thickness skin grafts are preferred and should be extended beyond the horizontal limb of the canthi to compensate for subsequent contraction of the graft. The preferred donor site is postauricular

skin, and even in young babies adequate skin is usually present. Other possible donor sites include skin from the supraclavicular fossa or upper inner arm. Our results show that this is an effective way of correcting the ectropion and poor lid closure, thereby preventing corneal exposure.

In long-standing and severe cases additional surgical procedures may be necessary fully to correct the ectropion. If excess lid laxity is present, a full thickness horizontal wedge resection can be performed at the same time as skin grafting, or may be necessary if the ectropion recurs. In other cases skin grafting with or without a horizontal lid resection may be combined with a lid lengthening procedure if correction of the ectropion alone does not result in adequate lid cover. The upper lid may be lowered, provided the skin shortage is also corrected, by tarsotomy, recession of levator palpebrae superioris, or scleral grafting, depending on the degree of lid lengthening required. The lower lid may be raised by interposing a scleral graft between the anterior lid retractors and the lower border of the tarsus.

The patient with ectropion who did not require surgery was an adult with involutional ectropion, which was not therefore associated with skin shortage.

In the older patient with Down's syndrome chronic blepharoconjunctivitis may lead to the development of cicatricial entropion and trichiasis. Four of our patients were adults with long-standing blepharitis, and all showed signs of corneal disturbance as a result of the trichiasis. If neglected, such corneal changes may progress and corneal suppuration develop.

Electrolysis may be used for single or aberrant lashes, but for large numbers it is time consuming, poorly effective, and may produce scarring of the tarsal plate. These cases are better treated with double freeze thaw cryotherapy to the lid margin.¹⁰ More severe cases of trichiasis and those with cicatricial entropion may be treated surgically as appropriate for the degree of scarring.^{11,12}

This study highlights the specific malpositions seen in patients with Down's syndrome and outlines an approach to the management of these problems.

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The Mersilene mesh sling—a new concept in ptosis surgery*

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SUMMARY The use of a Mersilene mesh sling in brow suspension ptosis surgery is presented. Seventeen cases of severe blepharoptosis have been treated by means of this sling with favourable results. Materials used in brow suspension procedures are categorised and discussed, and it is concluded that the Mersilene sling is an alternative to those currently available for the management of severe blepharoptosis requiring brow suspension surgery.

The use of synthetic non-absorbable macro-mesh materials has not previously been described in eyelid surgery. One such material is Mersilene mesh. It is a polyester fibre mesh manufactured by a machine knitting process which interlocks individual fibre junctions. This feature prevents unravelling and facilitates cutting of the mesh without disruption of adjacent fibre junctions.¹ Mersilene mesh has been used in a variety of clinical settings (Table 1). Workers in many fields, including Amis² and Peyman *et al.*,³ have shown histologically in animal and subsequent clinical studies that the mesh acts as a permanent scaffold supporting fibrovascular ingrowth. This feature represents an attractive concept to the oculoplastic surgeon with potential application in a number of clinical settings. Brow suspension ptosis surgery is one such. We have recently undertaken a clinical study aimed at evaluating the Mersilene sling. This paper outlines our initial findings.

Material and methods

We have used the Mersilene sling for correcting 17 ptotic eyelids in 11 patients—five children (age range 4 months to 3½ years) and six adults (age range 57–76 years). All the patients had severe ptosis with minimal or no demonstrable levator palpebrae superioris function. The aetiology of the ptosis was chronic progressive external ophthalmoplegia in six cases, congenital ptosis in four, and trigemino-

Table 1 Clinical applications of Mersilene mesh

1	General surgery:	diaphragmatic defects hernia repairs rectal/urogenital slings
2	Vascular surgery:	vascular prostheses
3	Orthopaedic surgery:	ligament/tendon repairs/replacement

oculomotor synkinesis in one. The eyelid occluded the visual axis in every case. In all the children urgent surgery was indicated to prevent or minimise the development of amblyopia; the adults requested surgery for functional reasons. Four patients had undergone previous brow suspension surgery by stored human fascia lata, but the ptosis recurred within three months in all of them. One patient with chronic progressive external ophthalmoplegia had had successful levator surgery some 10 years previously. The ptosis gradually recurred as the underlying disease progressed.

The surgical technique is a modified Fox's method as described by the senior author.⁴ Stab incisions are made in the eyelid and brow (Fig. 1). The lid incisions are made 3–7 mm from the eyelid margin in an attempt to match the position of the contralateral skin crease. The lid is divided into thirds, with incisions being made at the junction between the lateral and central thirds and the central and medial thirds. The medial and lateral brow incisions are made within the superior hair line of the eyebrow above the medial and lateral canthal positions. The superior brow incision is made midway between the two lower incisions, 7–10 mm above the brow. The position of the stab incisions is important. A peaked

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Fig. 1 Diagram illustrating position of stab incisions.

or flat lid contour is avoided and satisfactory lid lift is obtained by means of these guidelines.

The sling is easily cut from a sheet of Mersilene mesh to the approximate dimensions of 15 cm long by 5–7 mm wide (Fig. 2). The individual mesh pore configuration is oval; it is critical to cut the sling along the long axis of adjacent ovals until the required length is obtained. If the mesh is cut at right angles to this, a very stretchable and much weakened strip is fashioned. The sling is autoclaved and packaged prior to use. When required it is soaked in a suitable antibiotic solution for 5–10 min and then washed thoroughly in sterile saline.

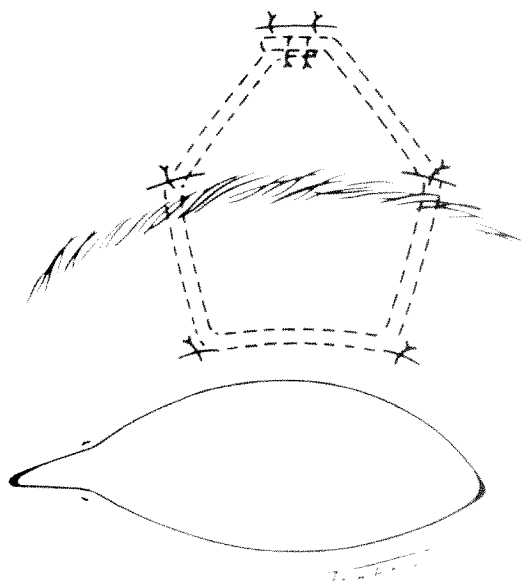


Fig. 3 Diagram illustrating Mersilene sling in position and sutured superiorly.

The mesh is threaded through the lid in the suborbicularis plane with a Wright's fascial needle: the two ends are brought through the superior brow incision. The sling is pulled tight. When the required lid height is achieved, the two strips are held taut, side by side, and secured using two 5 'O' Ethibond sutures passed through the mesh just within the brow incision, care being taken not to catch inadvertently the tissues with the suture. The excess mesh is trimmed and the sling is allowed to retract into the

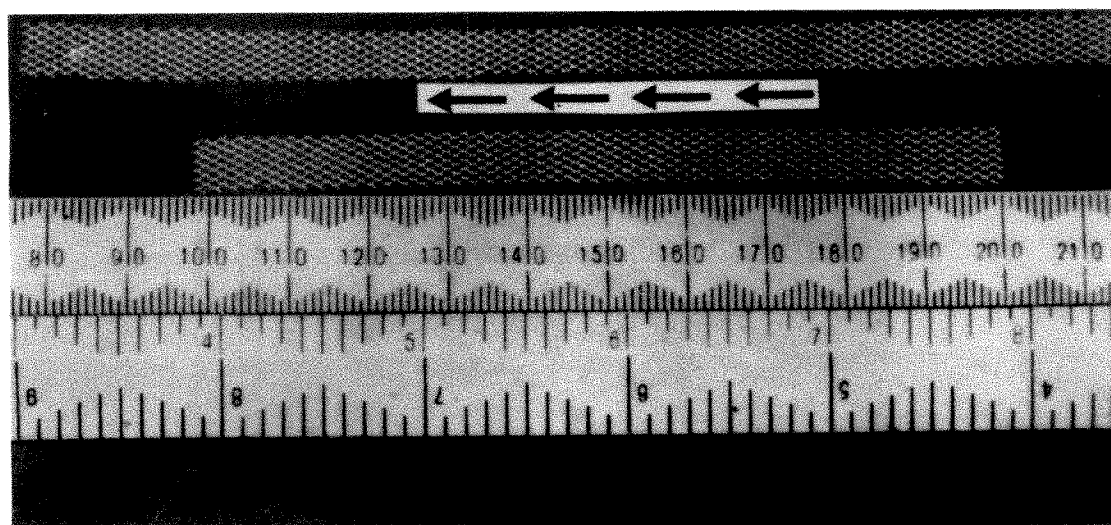


Fig. 2 Photograph demonstrating dimensions of the Mersilene sling. The long axis along which the mesh should be cut is arrowed.



Fig. 4 Right congenital ptosis preoperatively.



Fig. 5 Same patient as Fig. 4 postoperatively.

deep tissues of the brow (Fig. 3). The brow incisions are closed and a Frost suture, if appropriate, applied. Oral broad spectrum antibiotics are prescribed for one week postoperatively. Topical antibiotics and lubricants are routinely used for the first week and then as required.

Results

In all patients a significant improvement in lid height has been achieved. Figs. 4–7 illustrate two such cases. The improvement in the vertical palpebral aperture ranged from 2 to 5 mm (average 3.5 mm). The lid height obtained within one week has been maintained in all patients. The period of follow-up currently ranges from one to six months (average 10 weeks).

We encountered only one significant complication, namely that of a patient in whom a preseptal cellulitis developed several days postoperatively. This settled fully on systemic antibiotics, and removal of the mesh was not required. The case was complicated by two factors. At the time of operation the patient had an early respiratory tract infection and routine post-operative antibiotics were inadvertently not prescribed. β -Haemolytic streptococci of the same strain were grown from sputum and wound cultures. The patient has had no further problems for over three months. Recently a successful and uncomplicated

brow suspension procedure was undertaken with a Mersilene sling for severe contralateral ptosis.

Three patients developed mild exposure keratitis immediately postoperatively. All were successfully treated with topical lubricants, which one patient has continued to use as required.

Discussion

A wide variety of materials has been employed for brow suspension ptosis surgery (Table 2). These may be broadly divided into two groups—grafts and synthetic materials. Fresh autogenous fascia lata is a syngeneic graft and as such provides the best results in terms of both maximal duration of effect and minimal complications.^{4,7} It does, however, have certain disadvantages. The patient's leg needs to be large enough for adequate fascial harvesting, a procedure which in itself involves a separate operation on the leg; controversy exists on the best means of obtaining such tissue to minimise complications. General anaesthesia is invariably required. All the available alternative materials have certain disadvantages in terms of duration of action and/or unacceptable rate of extrusion.^{5,7}

In all our cases the use of fresh autogenous fascia lata was deemed inappropriate. The patients were either too small for adequate fascial harvesting or had requested that the procedure be performed under



Fig. 6 Patient with chronic progressive external ophthalmoplegia and bilateral ptosis preoperatively.



Fig. 7 Same patient as in Fig. 6 postoperatively.

Table 2 Brow suspension: materials

<i>Grafts</i>
Fascia lata: fresh autogenous
preserved human
bovine
Strips of skin/orbicularis/frontalis
Strips of fresh/preserved sclera
<i>Synthetic materials</i>
Silicone rod/band
Gold/silver/platinum implants
Sutures: Supramid
silk
polyester
Gore-tex soft tissue patch

local anaesthesia. The use of a general anaesthetic coupled with a separate operation on the leg was thought to be contraindicated in the remaining cases.

Theoretically an inert non-absorbable material which provides a meshwork scaffold for fibrovascular ingrowth and subsequent incorporation into host tissues would be valuable in brow suspension ptosis surgery. Several materials are manufactured in a mesh form. Nylon has been shown to lose strength after implantation and produces less regular collagen adhesions than polyester.⁸ Metallic meshes create a marked tissue inflammatory response, and the sites of fibre junction are subject to stress fatigue. Carbon fibre materials fragment at around three months after implantation, and a progressive resorption of surrounding collagen occurs as a consequence of the inflammation created by this breakdown.²

Gore-tex has recently been used in brow suspension ptosis surgery by Morax and coworkers.⁹ The Gore-tex soft tissue patch is a sheet of expanded polytetrafluoroethylene, a polymer familiar to many as Teflon. The manufacturers claim that the porous microstructure allows cellular penetration and thus incorporation into the surrounding tissues. Morax *et al.* cite a 10% extrusion rate within three months postoperatively in ptosis surgery, which allowed histological examination of the Gore-tex patch. They 'noticed the presence of vascular connective tissue rapidly surrounding the implant, with however, the possibility of separating easily this implant from the sub-cutaneous tissue'. This suggests less than complete tissue integration, with Gore-tex in such a situation acting more as a solid sheet than a true micromesh. If this is indeed the case, then the major advantage of Gore-tex over other synthetic materials would appear to have been lost. In comparison with the Mersilene sling, Gore-tex is significantly more expensive and the surgical technique of implantation more complicated; we do not consider it offers any advantages.

The initial results obtained with the Mersilene sling suggest that it is a real alternative to all those

Table 3 Mersilene mesh

<i>Advantages</i>	<i>Disadvantages</i>
Readily available; inexpensive	Foreign material
Easily prepared and implanted	?Long-term results in ptosis surgery
Strong, flexible, durable	
Permanent scaffold for fibrovascular ingrowth	
Clinically tried and tested	

materials, both allogeneic and xenogeneic grafts and synthetic substances, available for use in brow suspension ptosis surgery. When analysing the improvement in lid height attained, it must be remembered that an adequate rather than maximal lid position was the aim in those patients with chronic progressive external ophthalmoplegia (over 50% of our cases) in an attempt to minimise or obviate postoperative exposure problems. The only significant complication, namely that of a preseptal cellulitis in one case, might have occurred with any material in the particular circumstances. The advantages and disadvantages of Mersilene mesh are summarised in Table 3.

Further studies are necessary to evaluate the long-term results with the Mersilene sling. In the light of our initially favourable results we are conducting such an evaluation.

The Mersilene mesh sling has been used to correct 17 cases of severe blepharoptosis. The results obtained to date are most encouraging and compare very favourably with currently available materials used in brow suspension ptosis surgery.

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Separable evoked retinal and cortical potentials from each major visual pathway: preliminary results

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SUMMARY Single cell experiments in primates show that there are two major parallel pathways named after the lamination in the lateral geniculate nucleus. Each of these systems can be preferentially excited by appropriate stimuli. Here we report that in man the polarity of the evoked potentials both in retina and in cortex depends on which of these pathways is stimulated. The identification of the resulting waveforms is thereby simplified—a matter of practical importance. The fact that at retina and cortex there are characteristic potentials may reflect the different cell biology of the two pathways.

Several parallel visual pathways run from the retina to the primary visual cortex and beyond. In the cat the distinction is based on the concept of a linear (X) versus non-linear (Y) response to light and to pattern. In the primate retina there is an additional complication, for about 90% of all retinal ganglion cells are colour coded and can be recognised on flatmounts as smaller 'beta' cells. They almost all project to the parvocellular layers of the lateral geniculate nucleus (LGN). The larger alpha cells project to the magnocellular layers.

Recordings from the LGN and the retina suggest that the larger ganglion cells respond poorly to coloured objects present on an equiluminant background of different colour but are sensitive to motion, flicker, and luminance spatial contrast.¹⁻⁴ The smaller ganglion cells are better represented in the fovea, have smaller receptive fields, respond relatively poorly to achromatic flicker, and nearly all are colour coded, about 90% being of the red-green opponent type.⁵⁻¹² This subdivision is preserved in the cerebrum. The two subsystems project to different layers of striate cortex, and cytochemical techniques show that subsequent information processing occurs in segregated portions of the visual cortex.¹³⁻¹⁵ The colour coded cells are strictly linear. About 25% of the magnocellular layer cells (achromatic) are non-linear.

Recently Kaplan and Shapley² and Shapley and Perry¹⁶ have proposed a scheme to explain the

differences and similarities between cat and primate visual systems. They propose that the primate equivalent of the cat X and Y system project to the magnocellular layers of the LGN. The additional colour coded, linear system, which is so prominent in the monkey and so sparse in the cat, projects exclusively to the parvocellular layers of the LGN.

The foregoing differentiation was established by single cell recordings in subhuman species¹⁻¹⁸ and might be thought to have little bearing on clinical work or human experimentation, but psychophysical studies show that selective stimulation of the two pathways gives rise to differing sensations in the human subjects.¹⁹

We have investigated the possibility that there are electrophysiological correlates of these systems which can be recorded under clinical conditions.

The pattern electroretinogram (PERG) is recorded from the cornea. It should not be confused with the ERG evoked by flashes, which is produced by Müller cells in the outer retina. The PERG consists of two components, respectively cornea positive and negative (P₅₀ and N₉₅),²⁰⁻²² both of which are generated in the inner retina. The former is partly developed by retinal ganglion cells,²¹⁻²⁷ and the latter is associated with the activity of the optic nerve.^{21 22 28} The PERG evoked by black-and-white patterns is partly pattern specific and partly evoked by local changes in luminance. When a chequerboard reverses, the increase in brightness of part of the screen is exactly matched by decreases in other parts. It follows that the average response of many different

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areas as seen in the PERG should be zero, if the response to increments of light was exactly equal and opposite to that for decrements. This is characteristic of a linear system. The fact that the PERG can be recorded is thus evidence of a non-linearity, which we know now has its cellular correlate in the M_y cells. Although single cell recordings show that individual P_x cells have a strictly linear organisation, the recordings of summed potentials might reveal some non-linearities. Thus the effect of alternating isoluminant colours is of special interest. Furthermore there is little information about the effectiveness of motion in evoking a PERG.

The records from scalp electrodes, the visual evoked cortical potential (VECP), vary with the type of stimulus: triphasic waves, predominantly positive (P_{100}) are associated with pattern reversing stimuli and a complex sequence (C_0-C_3) with the appearance of a monochromatic pattern.²⁹ The effective stimulus is not luminance but border contrast. The different waveforms associated with various patterns may be due to the fact that, as the pattern is altered, the cortical region generating the response also changes. Thus the large foveal projection into area 17 is at the posterior tip of the calcarine fissure, while the remainder of the visual field is represented by cortex buried in the fissure: the magnitude and even the polarity of the VECP evoked from peripheral retina might therefore be different to that from the fovea. The surface of the adjacent occipital cortex (area 18) has cells with differing properties. Another reason for the various types of evoked potential is that groups of cortical cells which respond selectively to motion may generate the responses to pattern reversal, which can be considered as the equivalent of two patterns moving in opposite directions. When coarse reversing patterns are viewed, the impression of motion is overwhelming, but for finer patterns the percept is quite different. Thus altering the size and reversal rate of a pattern can change the type of cortical element responding. Other distinctions can be made: for example cells responding preferentially to motion of large objects are likely to be found extrafoveally and in area 18. Again the projection of the fovea is relatively deficient in blue-yellow sensitivity.³⁰ Although it has been reported that colour-specific VECPs can be evoked, there is little information about the waveform, since early work used a technique (steady state recordings) which obscured waveform characteristics.

In the present report, we show that when PERG and VECP are tested with combinations of patterns in which appearance and reversal are combined with luminance contrast or isoluminance colour contrast. The waveforms and other properties of the evoked potentials change in ways which strongly suggest that

the functional division of the visual system can also be demonstrated by these two non-invasive electrophysiological procedures.

Using equiluminous colour contrast stimuli simplifies the responses, a finding which is not only of practical interest. For these reasons we report our preliminary findings, since the complete analysis of cortical responses is a very complex matter.

Material and methods

The three authors and three other subjects provided the records described below. All had acuity corrected to at least 6/6. Five had normal colour vision and one a mild red-green defect. PERGs and VECPs were recorded simultaneously with gold foil and Ag/AgCl electrodes respectively. Gold foil electrodes were hooked in the lower fornix of the eye. The reference of the PERG was fixed to the ipsilateral temple. This electrode position reduces contamination of the PERG by remote cortical evoked potentials.^{31,32} Each record was an average of more than 1000 and less than 1200 responses.^{33,34} The electrical responses were amplified 100 000 times, with a bandpass of 0.3–100 Hz. The stimuli were generated on a TV screen which subtended $22 \times 16^\circ$ and was placed 1.6 m from the subject's eye. The monitor used was of studio grade A quality (Electronic Visuals 5100), and was driven by a PLUTO colour graphics peripheral (IO Research Ltd). This has 8-bit digital to analogue converters for red, blue, and green channels. All pattern changes occurred during frame blanking periods. A trigger pulse was developed at pattern onset or at each reversal, and used to initiate an averaging procedure in a PDP 11/23 computer. The appropriate TV signals were calculated by a computer program. All colours were isoluminant (44 cd/m²) and lay on protan or tritan colour confusion lines. Red-green or blue-yellow (RG or BY) patterns appeared from a uniform background in such a way that the average brightness and colour of the light emitted by the TV screen did not alter when the stimulus appeared (calibrated with a Minolta CS 1000 photometer: in addition we checked that neither the hue nor the luminance of a card illuminated by the TV-screen altered as the screen image changed). The CIE co-ordinates for red were $x=0.347$, $y=0.483$, for green $x=0.510$, $y=0.390$, for blue $x=0.302$, $y=0.222$, and for yellow $x=0.443$, $y=0.445$. For the RG stimulus the background co-ordinates were $x=0.438$, $y=0.428$ and for BY $x=0.350$, $y=0.301$. Patterns appeared for 200 ms and were replaced by a yellowish white or bluish white background for 600 ms or reversed abruptly every 400 ms. Square wave gratings were used with a spatial frequency of 0.38 to 13.2 c/degree (for further details see Arden *et al.*^{35,36}).

Results

The columns of Fig. 1 show responses recorded from the cornea, evoked either by the appearance of a pattern or by pattern reversal. The rows show various combinations of colour and luminance contrast. The appearance of a red-green coloured pattern should preferentially excite the smaller colour coded cells. It produced a small cornea negative response. Pattern reversal also evoked a negative response in the retina: the stimulus here would also be expected to excite preferentially colour coded cells.

The responses to blue-yellow stimuli were too small to be detected (less than the noise level, which is $\approx 0.3 \mu V$), probably because the proportion of retinal cells which respond to yellow-blue is only 5–10% of all colour coded cells.

The stimulus change from colour contrast to luminance contrast was achieved by moving the green grating through 180° of phase and thus adding it to the red. The stimulus then became black-yellow

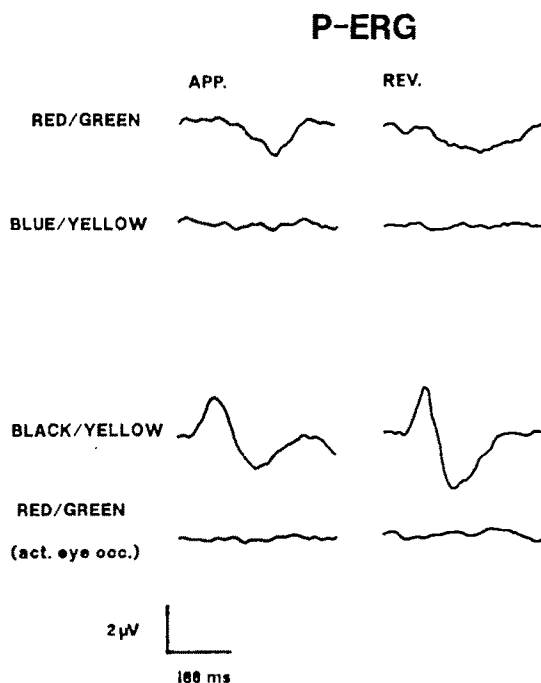


Fig. 1 Pattern electroretinograms to coloured stimuli are shown (stripe sizes 1.5 cycles/degree). Only negative responses were recorded for the red-green isoluminant gratings (row 1), while no response was found for isoluminant blue-yellow gratings (row 2). When luminance contrast was used (row 3) the typical PERG was recorded. Note the early positive component which is followed by a negative component. Row 4 demonstrates, that no response is recorded when the eye with the gold foil electrode is occluded.

(row 3). Green-black or red-black patterns gave qualitatively the same results as black-yellow or black-white. The waveforms elicited in the retina were now quite different: biphasic positive-negative pattern ERGs were seen. In row 3 there is a local luminance change, but from the standpoint of an individual retinal neurone, with for example green cones feeding the receptive field centre, the change in the isoluminant red-green pattern will also represent a change in excitation: therefore the very large difference between the PERGs in rows 1 and 2, on the one hand, and row 3 on the other, requires explanation (see Discussion). Row 4 shows the responses obtained when the stimulus fell only on the fellow eye, while the eye with the gold foil electrode was occluded. No voltage changes were seen, showing that remote recording of the VECP (or the response of the fellow eye) was minimal.

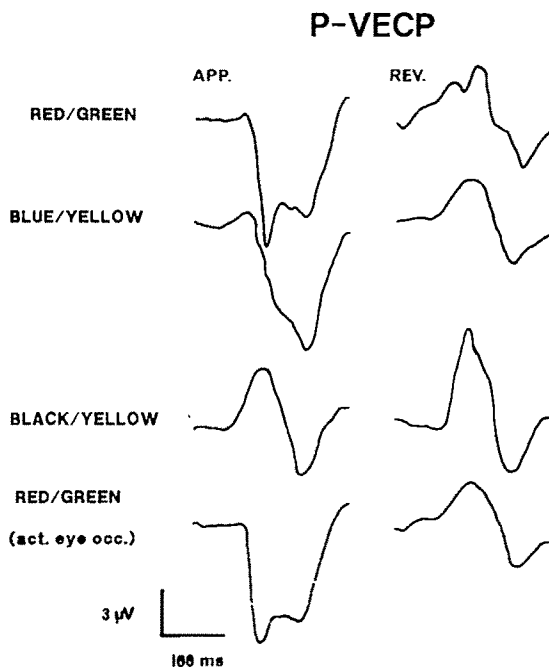


Fig. 2 Visual cortical evoked potentials under the same stimulus conditions as in Fig. 1. Surface positivity gives an upward deflection as shown. For isoluminant gratings a significant difference between appearance and reversal mode can be seen. For both red-green and blue-yellow gratings (rows 1 and 2) a large negative response is found, with an early maximum for red-green and a late maximum for blue-yellow. Note that, unlike the PERG, reversal of a coloured pattern produces a VECP with an early positive component. Similar responses are also found for black-yellow stimuli (row 3). No significant change can be observed when the subject fixates the screen with one or the other eye (compare rows 1 and 4).

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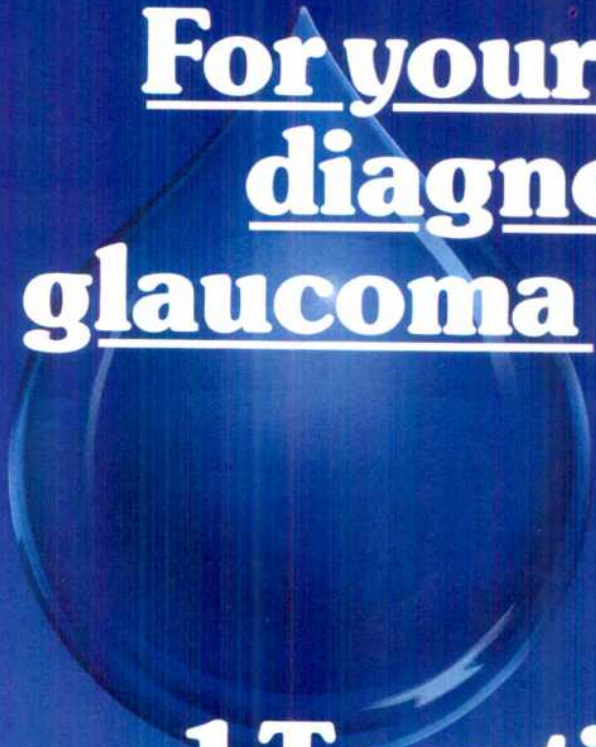
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Mills, K.B. et al. British Journal of Clinical Practice, 1987; Supplement 50, **41**: No.6, 10-12.

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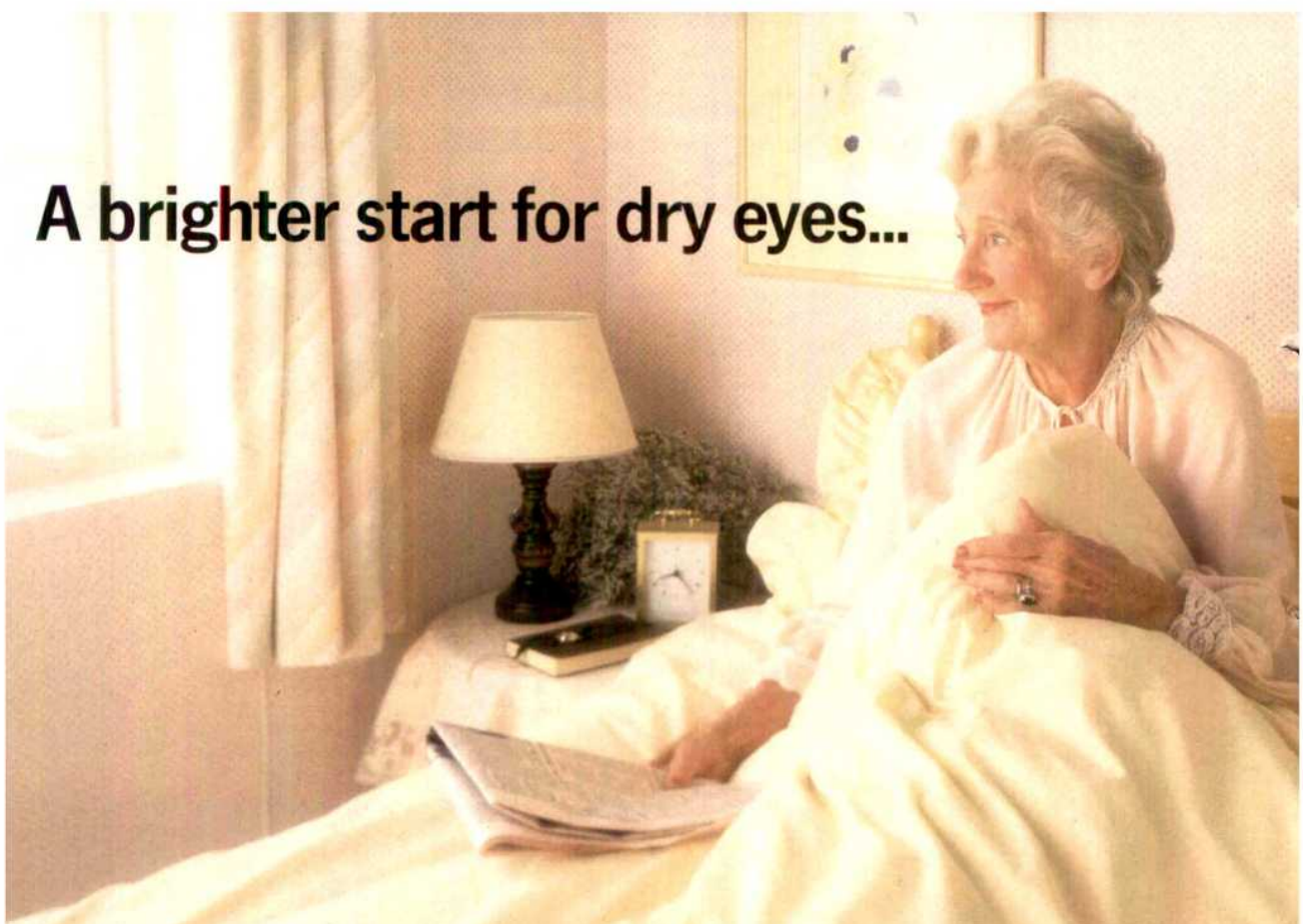
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Fig. 2 shows the VECPs associated with the same stimuli. The black-yellow reversal (row 3) represents the condition which is most familiar, a pattern formed by local changes in luminance. Note that for both appearance and reversal there was a surface positive response (P_{100}) followed by a later negativity. The stimuli used were of relatively low spatial and temporal frequency. Such stimuli excite the illusion of motion, and it is considered that the accompanying VECp was produced by a motion and contrast detecting system.³⁷ Motion is preferentially detected by the magnocellular system. Isoluminant red-green and blue-yellow gratings also produced large cortical responses, in contrast to the small voltages elicited in the retina (see Fig. 1). However, the effect of reversal and pattern appearance are quite different. The reversals under these experimental conditions evoked surface positive responses (like the luminance contrast patterns), but the appearance responses were of opposite polarity. The timing of the response to blue-yellow was delayed relatively to the red-green. Note that the first and

fourth rows give very similar VECPs, since the cortical mechanisms can be excited from either eye.

Fig. 3 shows how the waveforms of the VECPs change with spatial frequency. For red-green patterns the appearance response was always negative, but the reversal response changed from positive to negative as the spatial frequency increased. The perceptual correlate of this change is that the higher spatial frequency gratings do not appear to 'drift' like the coarser ones. Reversing blue-yellow gratings gave surface positive waves. For higher spatial frequencies these responses were greatly attenuated. This is in part due to the effect of the longitudinal chromatic aberration of the human eye, which³⁸ amounts to over 1.5 D for the blue light emitted by the monitor. Consequently, the blue bars in a blue-yellow grating are defocused, and the contrast at 4 cycles/degree would be considerably reduced. The yellow bars are in focus, and therefore on the retina; the yellow-blue stimulus is reduced to a change in yellow luminance. It is difficult to calculate the exact change in luminance contrast caused by this

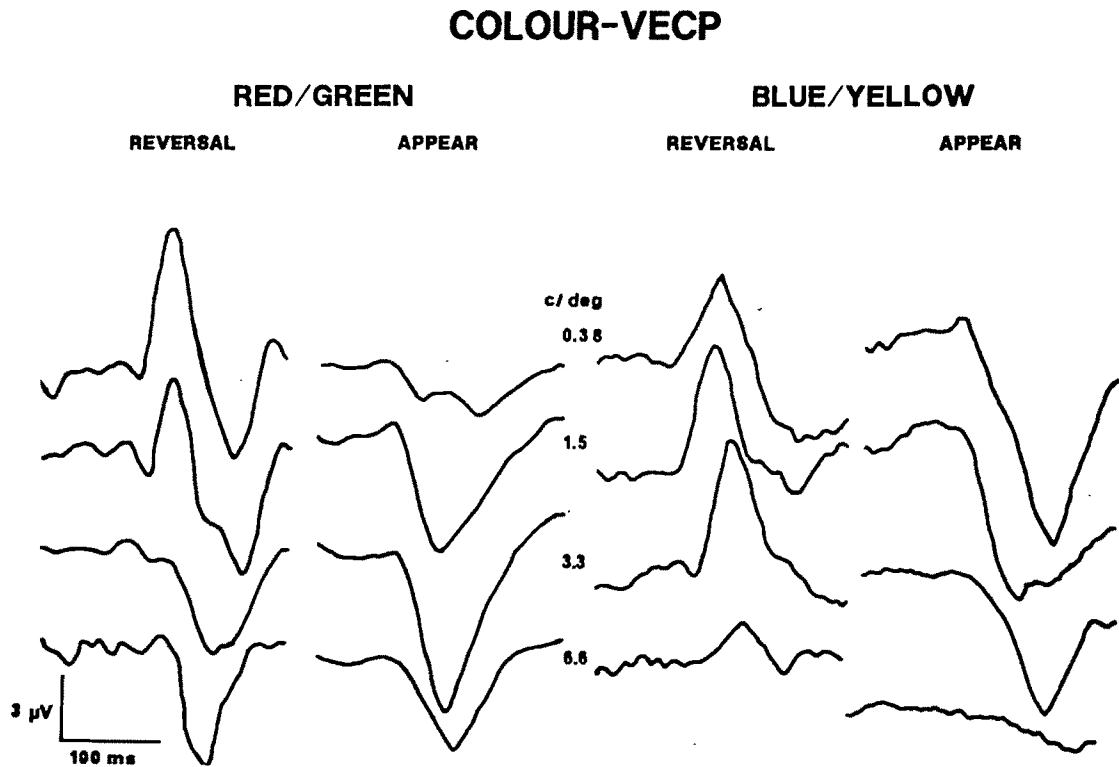


Fig. 3 VECp responses to isoluminant gratings of various stripe sizes are shown. Note the loss of the early positive component for higher spatial frequencies for the reversal mode (column 1). For red-green appearance (column 2) only negative response were recorded. The maximum amplitude occurs at 3.3 cycles/degree. By contrast for blue-yellow reversal (column 3) a positive component is found for all spatial frequencies. For pattern appearance (column 4) blue-yellow also shows a negative component which peaks at low spatial frequencies (0.38 cycles/degree).

COLOUR-VECP

RED/GREEN

MIDLINE

RIGHT
HEMISPHERE

2 c/deg.

0.5 c/deg.

BLUE/YELLOW

MIDLINE

RIGHT
HEMISPHERE3 μ V

100 ms

Fig. 4 Midline and right hemisphere responses for two spatial frequencies are shown. Note that for red-green the maximal response is found in the midline and for higher spatial frequency while for blue-yellow there is no significant amplitude difference between midline and periphery. (For this subject the response is even slightly larger in the hemisphere.) Further, the red-green response in the midline line peaks early at about 135 ms. The maximum amplitude for the red-green response in the hemisphere peaks later (about 190 ms). For blue-yellow the maximum response peaks significantly later, both in midline and hemisphere.

chromatic aberration. Campbell and Green's³⁹ data on defocus suggest that a blue-yellow grating of 6 c/degree would be demodulated by over 90%. We could not obtain any definite appearance response with patterns of >4 c/degree, and this is consistent with the stimulus producing a colour-specific response.

Fig. 4 compares other aspects of the VECPs with colour appearance. Note that the red-green patterns always evoked a response which peaked at about 40 ms before the yellow-blue. Red-green patterns produced larger responses to higher spatial frequencies (2 c/degree) than did the blue yellow (0.5 c/degree). In addition, while the largest red-green response was obtained at the midline, 2 cm above the ionion, the blue yellow response was as large, or larger on the hemisphere 5 cm lateral to the midline.

Fig. 5 shows the relative amplitude for red-green

gratings from a subject with red-green deficiency compared with the average for three normal persons. The maximum amplitude of the response was normalised to 100 in each of the three normal persons and the red-green defective subject. (The responses — see figs. 3 and 4 — have different components, and these are identified on the figures.) The lines indicate $+1$ SD. The maximum response, at 135 ms, occurs at the midline for all three normal persons.

The 25-year-old colour-defective has normal 6/6 vision when wearing glasses. His colour vision deficiency was first established with Ishihara plates (he could not read number 3), and the colour contrast sensitivity measurements confirmed this. The threshold for red-green was 12%, while the average normal value ranges from 3.5–7.5% with a mean of 5% (for details about this test see Arden *et al.*^{35,36}). His maximal response was found to be the late component (N-195) (see below). At 135 ms the

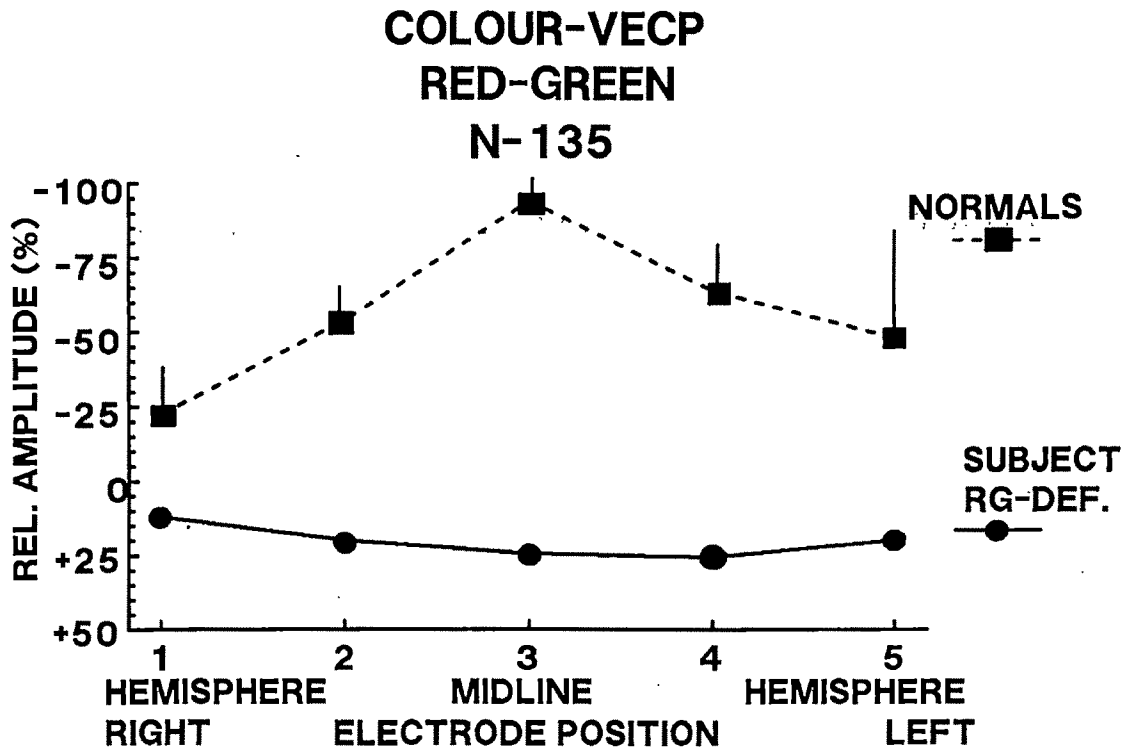


Fig. 5 Relative colour appearance VECP amplitudes of three normal persons (dotted line) and a subject with mild red-green defect (solid line). The maximal amplitude of the whole response was set to 100%. for the normal persons the peak amplitude of the largest component was surface negative and occurred after about 135 ms after the pattern appearance of a grating with 3.3 cycles/degree. Note the larger amplitude at the midline electrode. By contrast for the same stimulus conditions the colour defective subject had a relatively small amplitude response which was of inverted polarity (surface positive). RG-def. = red-green defective.

response was much smaller and the polarity was surface positive—that is, inverted with respect to the normal. There was no change in voltage with electrode position.

Fig. 6 shows the later N-195 responses for the subject and normal persons: negative polarity was found for both, but for the colour defective subject the responses were much larger. Note that, again, there is no sharp localisation of the response to the midline.

Fig. 7 compares the results from the same three normal persons and from the colour defective subject for blue-yellow gratings. The maximum response was found for all in the late component and for low spatial frequency. The result from the colour defective subject fell within the normal range.

Discussion

PATTERN ERGS TO COLOUR AND LUMINANCE

When equiluminous colour contrast is used, the PERGs are very small and surface negative. Blue-

yellow, in particular, produces no measurable response. In contrast the cortical responses are large: evidently there is some selective 'amplification'.

It is considered that colour coded cells in the retina (P cells, or beta ganglion cells) have linear characteristics—that is, they sum excitation and inhibition in a linear fashion. The proportions of ganglion cells with receptive field centres which respond to red and to green are roughly equal, and the proportion of cells which are excited by the increase of red light is nearly the same as the proportion excited by a decrease of red light (and the same is true for green). Colour coded cells have surrounds of opposing potentiality, but the balance between the two varies considerably in a random manner (the cells also lie at random positions with respect to the grating bars). It is evident that the net difference between excitation and inhibition caused by the change of the isoluminant coloured pattern should be nearly zero unless the cells had non-linear characteristics. Therefore it is not surprising that, although individual cells are greatly influenced by the

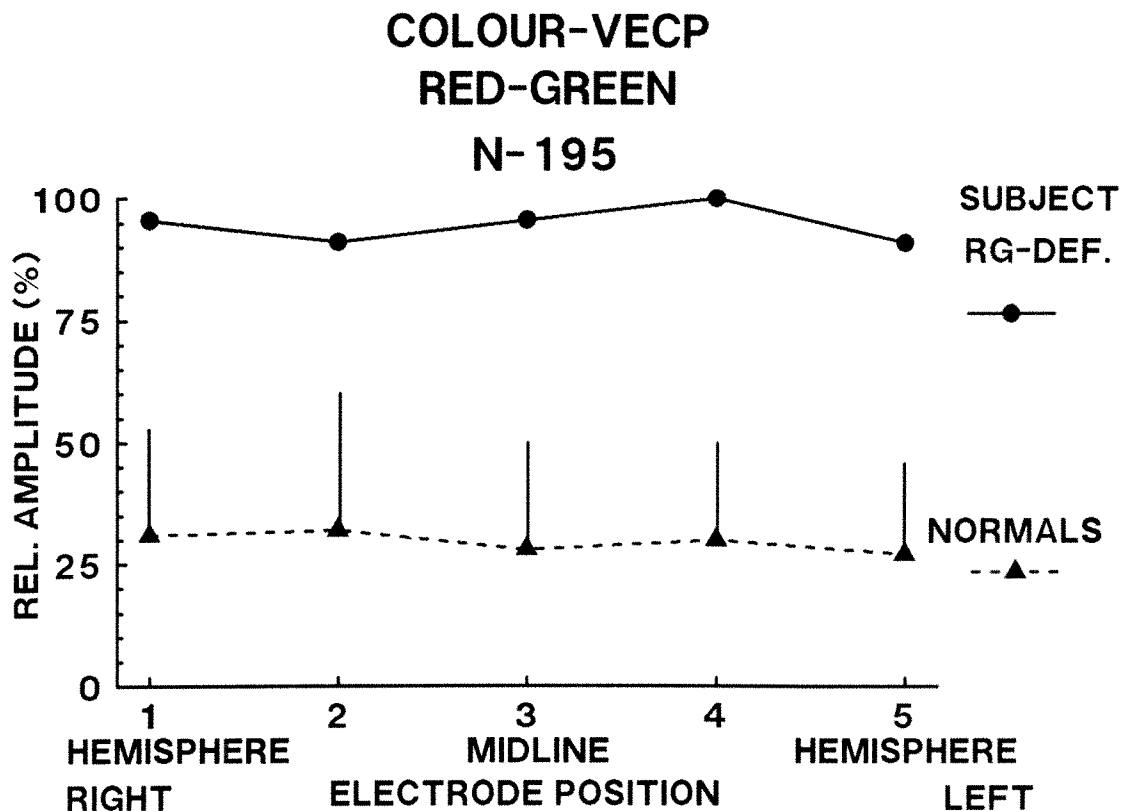


Fig. 6 Relative amplitudes for the late component (N-195) of the VECp elicited by red-green appearance. For the colour defective subject this was the largest response. The amplitude was nearly constant at all electrode positions. The relative amplitude of the late component in the three normals is much smaller (dotted line).

stimulus, the PERG is very small, which implies that the average state of the assembly does not change. The small responses we can see may be due to small departures from isoluminance or to the fact that not all classes of colour coding are equally represented.

However, this poses a further question: what does respond to the yellow black grating? All the arguments deployed above apply with equal force to yellow-black stimuli: we would expect a small or absent PERG. This is obviously not the case. It might be thought that the colour contrast (red-green) was not as intense a stimulus as the luminance contrast (black-yellow). The effective contrast change for reversals is, however, twice that for appearance. But, for every combination of colour or luminance, appearance and reversal produce equal amplitude retinal responses. A qualitative method of analysing the difference is as follows: for a 'green centre' retinal ganglion cell the red phosphor can produce very little excitation or inhibition at the receptive field centre; therefore the contrast will appear to be nearly 100%, as it is for black-yellow.

An alternative explanation which we favour is that yellow-black (like the black-and-white stimulus usually employed) stimulates a non-linearity in the responding retinal system, and indeed single cell recording has revealed a non-linearity (M_V cells) in the magnocellular layer. Non-linearities have frequently been demonstrated for the PERG evoked by black-and-white patterns, but Arden and Vaegan³⁴ failed to find non-linearities when using red-green patterns. If this is the explanation, then it follows that the positive portion of the PERG must be produced by a retinal system which includes such a non-linearity—that is, by non-colour coded (alpha) cells.

Korth and Rix⁴⁰ have evoked pattern ERGs with very intense isoluminous red-green patterns (22 500 td, that is, 3183 cd/m² for a pupil diameter of 3 mm or 1790 cd/m² for a pupil diameter of 4 mm in comparison with our mean luminance of 44 cd/m²), and found the usual positive-negative waveforms. It seems likely that such intense stimuli could evoke activity in the achromatic channel as well as in the colour coded cells. Recently⁴¹ the same authors have used lower

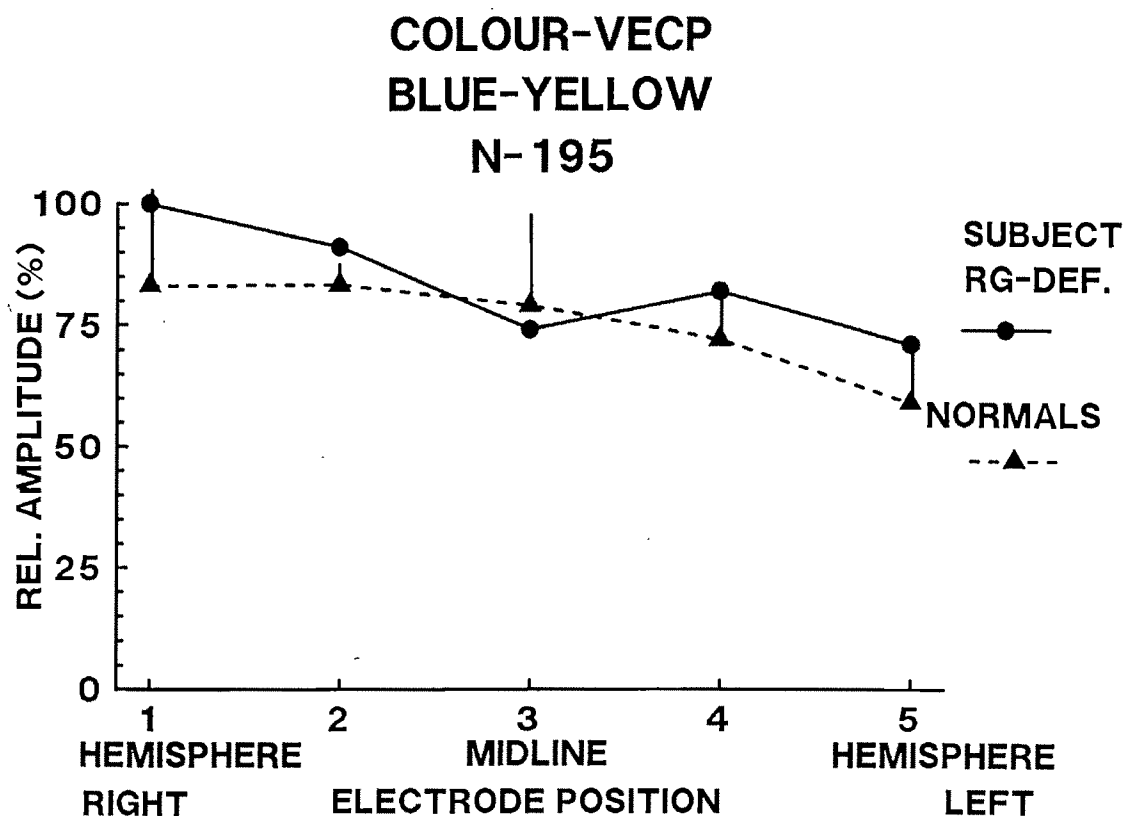


Fig. 7 Relative amplitude for blue-yellow colour appearance VECs. Maximal responses were found for both normal persons and a red-green defective subject at a low spatial frequency (0.5 cycle/degree). No influence of the electrode position on response amplitude can be observed, and both normal and defective persons gave similar results.

luminances, and with desaturated stimuli; their results are similar to those reported here.

THE VECP TO APPEARANCE

In the cortex VECs evoked by isoluminant coloured gratings produce quite different responses to patterns in which there is luminance but no colour contrast. The VEC waveform and amplitude is somewhat variable from subject to subject, but the variations shown in Figs. 2, 3, and 4 are reproducible from subject to subject, and alteration of the stimulus causes predictable changes. In many circumstances isoluminant colours produce simple surface negative waves. Murray *et al.*⁶ have shown similar results for red-green gratings and report that strict isoluminance is required for the negativity to be uncontaminated by positive components. Apparently the same is true for blue-yellow. In addition responses to blue yellow stimuli vanish for higher spatial frequencies at which blue modulation is diminished. Since only the fovea can resolve higher spatial frequencies, this may be an electrical demonstration of foveal tritanopia.³⁰ Thus

it appears that there are specific cortical responses to colour contrast patterns of low and mid range spatial frequency colour contrast. The responses to blue-yellow and red-green are also easily distinguishable —by their timing and by the relative scalp location of the maximum voltage and their spatial tuning. It is interesting that there are perceptual differences in reaction time which correspond to the different peak times of the evoked potentials (EPs).⁶ Further work is required to determine whether these differences are due to gross differences in the cortical sites which generate the potentials.

THE VECP TO REVERSAL AND MOTION

When colour contrast gratings have low spatial frequency and are used in the pattern reversal mode, they produce the sensation of motion like monochromatic patterns, and the VECs evoked resemble the VECs produced by monochromatic patterns. It is known that the amplitude of such responses (to pattern reversal) varies with spatial frequency, but calculated spatial frequency for zero amplitude does

not correspond to visual acuity. A much closer correlation is obtained with pattern appearance. Hence it is often suggested that the pattern reversal VECF evoked by coarse patterns is related to motion detection. This strongly suggests that the specific negative responses produced by the isoluminous coloured patterns, in appearance mode, may correspond to the operation of the parvocellular system. Consistent with this view is the finding that achromatic patterns (provided the spatial frequency is sufficiently high) may also evoke surface negative EPs.^{44,45}

Thus all the observations indicate that the use of patterns containing colour or luminance contrast may distinguish between two parallel visual systems. This raises the further possibility that the structural organisation of parvo- and magnocellular pathways, or the different neurotransmitters, account for the polarity differences in the evoked potentials: in any case, the novel evoked potentials produced by colour may assist in understanding a variety of ophthalmological and neurological conditions.

CLINICAL DATA

Regan⁴⁶ as well as Murray *et al.*⁴² examined a deuteranopic patient with red-green gratings and did not record any response when the gratings were isoluminant. We examined a subject with mild red-green deficiency and observed that the VECF response to red-green gratings had a completely different configuration when compared with that of normal persons, though blue-yellow gratings evoked normal responses. It is yet not possible to determine if there is a total loss of the N-135 component in the colour-defective subject while the N-195 remain unchanged or whether there is a significant delay of the N-135.

It has been shown that hereditary colour vision defects can be detected by colour VECFs. Detection of acquired colour vision, however, is of more clinical importance. The ability of the colour VECF for this purpose has to be shown in future research.

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Value of the ERG in congenital nystagmus

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From the Birmingham and Midland Eye Hospital

SUMMARY A group of 64 children with poor vision and early onset nystagmus were investigated retrospectively by the electroretinogram (ERG). Fifty-eight of these children also underwent analysis of the visual evoked potential (VEP), and 40 underwent colour vision analysis. Seventeen children were found to have complete congenital achromatopsia (rod monochromatism), being identified by their total colour blindness, reduced visual acuity, and reduced or absent photopic and flicker (30 Hz) ERGs. Two children with incomplete X-linked congenital achromatopsia were also found. This study identified the need to investigate children with nystagmus by means of the ERG and suggested that the ERG was useful where the diagnosis was uncertain, particularly at early school age. The incidence of congenital achromatopsia in a group of otherwise undiagnosed children with early onset nystagmus was high (29%), with 40% being classified as having congenital idiopathic nystagmus.

Nystagmus presenting in infancy, often referred to as congenital nystagmus, is a non-specific manifestation of a wide variety of disorders of the eyes, visual pathway, or central nervous system.^{1,2} The ophthalmologist is asked to assess the vision and identify any ocular causes. The diagnosis is straightforward when there are obvious abnormalities such as strabismus, aniridia, cataracts, or colobomata. However, there are a number of children where no gross eye anomalies can be found and there are no changes on general or central nervous system examination. In some of the children there may be a family history of nystagmus which may help with the diagnosis.³

Analysis of the type of nystagmus may give guidelines towards making the diagnosis. The 'searching' type is indicative of Leber's amaurosis or optic nerve diseases such as atrophy or hypoplasia,^{1,2} whereas the 'pendular' type of nystagmus is associated with ocular albinism, retinoschisis, achromatopsia, and congenital stationary night blindness (CSNB).^{1,2} Congenital idiopathic nystagmus (motor efferent) can often be identified by observing the point of reversal or null zone, together with any compensatory head posture, or the development of a jerky nystagmus on lateral gaze.¹

Ocular albinism may be identified by iris transillumination and foveal hypoplasia, together with abnormalities in the visual evoked potential (VEP).

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The clinical signs of foveoschisis, CSNB, and achromatopsia are not consistently present. Variability of clinical signs is a feature of conditions associated with early onset nystagmus and can lead to incorrect diagnosis.

Complete congenital achromatopsia (rod monochromatism) is considered by most authors to be a rare condition, having a prevalence of 1–3 per 100 000 of the normal population.⁴ The most extensive study of this condition to date was carried out by François *et al.*,⁵ who assessed 215 patients with congenital achromatopsia, and demonstrated an autosomal recessive inheritance.

More recently certain rare incomplete variants of congenital achromatopsia have been identified. In one of these variants the blue cones appear to be intact, the vision is fairly good, and nystagmus is minimal or absent; however, the electroretinogram (ERG) abnormalities are as severe as in complete achromatopsia. It is thought that this incomplete variant may be progressive, with an X-linked recessive inheritance.⁶ Although a history of photophobia, and reluctance to play in bright daylight, together with a fine (3°) nystagmus, is indicative of congenital achromatopsia,³ these findings are by no means consistent. Many authors, notably Harcourt,⁷ have recommended the use of the ERG in order to identify the complete or incomplete forms of congenital achromatopsia.

This study examines the use of ERG analysis in

classifying children who present with early onset nystagmus and suggests the value of obtaining such a classification for prognosis and genetic counselling.

Patients and methods

Sixty-four children or young adults (<18 years) with early onset nystagmus were assessed. They represented all such patients referred for electrodiagnostic assessment from April 1984 to May 1988. Thirty-six of the children were male and 28 female.

Every patient underwent assessment of visual acuity, fundus examination, and ERG (scotopic, photopic, and 30 Hz flicker). Fifty-eight of the children underwent VEP analysis, and 40 were assessed for colour vision. Colour vision analysis was obtained by means of a Farnsworth Munsell (F/100) colour test. None of the children in this study had colour vision assessment by means of the Sloan test,⁸ which has been reported by some authors as being useful in the diagnosis of achromatopsia. Of the 17 children with complete congenital achromatopsia 10 received genetic counselling, and therefore a full study of the family history.

ERGs were obtained under scotopic and photopic conditions, using a stimulus of 1200 lux. Where possible the scotopic ERG was obtained after 10 minutes' dark adaptation. Photopic conditions were ensured by adapting the patient with a 650 lux Ganzfeld light source. The flicker ERGs were recorded with a 30 Hz white light stimulus of 975 lux. Recording electrodes were of a Ag/AgCl electroencephalograph (EEG) type, and the active electrodes placed on the lower eyelids. Reference electrodes were placed on the outer canthus of either eye.

VEPs were recorded to flash stimulation only. Pattern reversal stimulation was thought to be inappropriate because it requires good fixation, which is negated by nystagmus. Two children were assessed by pattern reversal stimuli, and as their responses were absent no further children were thus assessed. Recording electrodes were placed on scalp positions Fz and Oz, according to the international EEG convention. Fz was connected to the positive side of the amplifier, such that all positive waves appeared in a downward direction.

The VEPs and ERGs were recorded using a Nicolet CA1000 clinical averager, and stimulus was provided by a Ganzfeld stimulator. VEPs and ERGs were analysed by peak to peak measurements of P2 waves and b waves respectively.

Results

Table 1 shows the breakdown of the diagnoses

obtained following electrodiagnostic assessment. The visual acuities in general were better in the children with idiopathic nystagmus than in those with complete congenital achromatopsia and Leber's amaurosis.

It can be seen from Table 2 that the ERGs were normal in the children with idiopathic nystagmus and ocular albinism. In Leber's amaurosis the ERGs were grossly abnormal to all stimuli. In the children with complete or incomplete congenital achromatopsia the scotopic ERGs were normal, and the photopic and flicker ERGs were grossly reduced or absent. Those with CSNB had ERGs with a short latency a and b wave to scotopic stimuli (similar to photopic ERG), and an abnormal a to b wave ratio, sometimes referred to as the Schubert-Bornsheim change. The child with foveoschisis demonstrated an ERG with abnormal a to b wave ratio to both scotopic and photopic stimuli (Fig. 1).

In seven of the eight children with ocular albinism the VEPs displayed contralateral enhancement—that is, the amplitude of the VEP was much greater from the hemisphere contralateral to the eye being stimulated than the VEP from the ipsilateral hemisphere. Four out of the seven children with Leber's amaurosis had reduced VEPs. The VEPs were normal in all the other groups of children.

Analysis of colour vision by the F/100 test revealed gross abnormalities in all the children with complete achromatopsia, but the abnormalities in the two brothers with incomplete achromatopsia were only mild, with a blue-yellow axis.

The family histories of the 17 children with complete congenital achromatopsia suggested an autosomal recessive inheritance in every case. Ten of the children presented with no known family history, five were male and five female. The other seven children with complete achromatopsia came from three families. One family included two affected girls and one affected boy, and the other two families each included one affected male and one affected female. Parental consanguinity was found in only two families, which is in contrast to the findings of François *et al.*⁵ and Bell,⁹ who reported parental consanguinity in 20–30% of families. The two children with suspected incomplete achromatopsia, were brothers, with no other family history, which was therefore consistent with an X-linked recessive inheritance.

All but one of the children with complete achromatopsia were attending normal schools without difficulty, and the two boys with the incomplete form were also attending normal schools. The one patient (aged 18) who had attended a school for the partially sighted stated that she was not as visually handicapped as her fellow pupils, and she considered this

Table 1 *Final diagnoses of children with congenital nystagmus in this study. Fundus, visual acuity, and inheritance*

Diagnosis	Visual acuity	Fundus appearance	Inheritance
Congenital achromatopsia (n=17)	6/36–1/60	Normal, occasional macular hyperpigmentation	Autosomal recessive
Incomplete congenital achromatopsia (n=2)	6/18–6/24	Normal	? X-linked recessive
Congenital stationary night blindness (n=1)	6/18	Normal	X-linked recessive
Ocular albinism (n=8)	6/18–6/36	Foveal hypoplasia (iris transillumination)	X-linked recessive
Leber's amaurosis (n=7)	6/36–<1/60	Optic disc pallor, narrow vessels, and/or peripheral or macular pigmentation. Two patients described as normal	Mainly autosomal recessive
Juvenile retinoschisis (n=1)	6/18	Foveoschisis, vitreous opacities	X-linked recessive
Congenital idiopathic nystagmus (n=28)	6/18–6/60	Normal	X-linked dominant

to be a disadvantage. She was previously diagnosed as having congenital idiopathic nystagmus.

Discussion

The results of this study confirm that the ERG using scotopic, photopic, and flicker stimuli is of value in classifying children and young adults with early onset nystagmus. This test is of particular value in differentiating between idiopathic nystagmus and complete or incomplete congenital achromatopsia, the absence or gross reduction of photopic and flicker ERGs being diagnostic in the latter conditions.

29% of the children in this study, who presented with unclassified early onset nystagmus, were after ERG analysis classified as having congenital achromatopsia. Although the result of colour vision

analysis was fairly typical of complete achromatopsia in this study, other authors have questioned the reliability of such techniques in identifying the condition. This has been partly resolved by the use of the Sloan colour test.⁸ However, many children are unreliable in subjective testing. An objective measurement such as the ERG is therefore of value and can be performed quickly and painlessly. Nevertheless colour vision testing remains an invaluable indicator of the incomplete forms of achromatopsia. The ERG also proves to be of value in the differential diagnosis of Leber's amaurosis (gross reductions to all stimuli) and in CSNB (Schubert-Bornsheim ERG). Analysis of the ERG waveform can also identify foveoschisis.

The VEP to flash stimulation would appear to be of value in cases of ocular albinism, and the finding of

Table 2 *Test results*

Diagnosis	Age (years)	Colour vision (F/100)	VEP (flash) (amplitude)	ERG		
				Scotopic	Photopic	Flicker
Congenital achromatopsia	2–18 x=11.3	534–850 x=608.4	6–24* x=12.4	43–102* x=68.3	2–8* x=3.8	0–2* x=0.6
Incomplete congenital achromatopsia	9–10 x=9.5	234–268 x=251.0	12–16 x=14.0	67–96 x=81.5	3–7 x=5.0	0–0.5 x=0.25
Congenital stationary night blindness	14	—	11–12 x=11.5	14–18† x=16.0	22–23 x=22.5	12–13 x=12.5
Ocular albinism	3–17 x=7.5	86–112 x=97.0	8–15‡ x=12.8	49–115 x=77.4	28–64 x=39.3	12–21 x=17.2
Leber's amaurosis	1–10 x=4.6	—	2–14 x=6.8	0–2 x=0.8	0–4 x=1.2	0–5 x=2.3
Juvenile retinoschisis (foveoschisis)	12	328	4–5 x=4.5	10–20§ x=15.0	11–16§ x=13.5	4–7 x=5.5
Congenital idiopathic nystagmus	2–18 x=8.4	67–178 x=105.0	6–28 x=12.5	45–97 x=68.7	16–43 x=26.8	5–14 x=9.6

x=Mean.

*Normal range for VEP=4–35 μ V.

Normal range for scotopic lid ERG=30–130 μ V.

Normal range for photopic lid ERG=15–65 μ V.

Normal range for flicker lid ERG=5–18 μ V.

†Schubert-Bornsheim change.

‡Most of these VEPs displayed contralateral enhancement of the P2 component, indicating misrouting of the visual pathways.

§Abnormal a to b wave ratio.

F/100 values are in terms of 'total error score'.

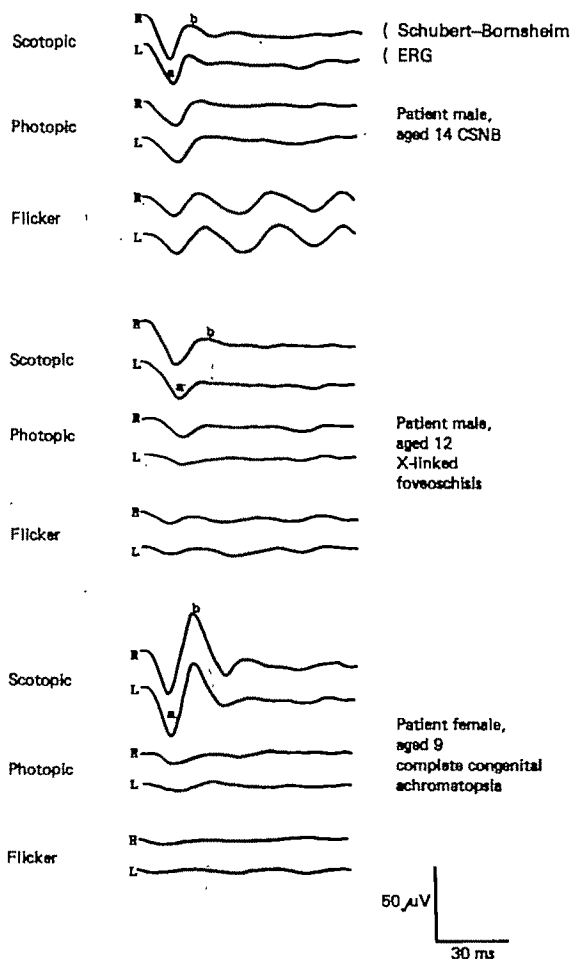


Fig. 1 ERG abnormalities in CSNB (shortened scotopic a and b wave, and abnormal a to b wave ratio), X-linked foveoschisis (abnormal a to b wave ratio), and congenital achromatopsia.

a normal flash VEP in children with congenital achromatopsia is interesting, particularly as the visual acuity was frequently less than 6/60. The use of pattern reversal stimulation is questionable,

since nystagmus makes accurate fixation difficult. However, such a stimulation may be a help to diagnosis in those children suspected of psychogenic visual loss.

Interestingly most children referred for investigation were of school age and many were in secondary school or had just left school. Only two children in the complete achromatopsia group were under 5 years old. It was apparent that the reason for referral was for diagnosis, so that advice on prognosis, future schooling and career, and inheritance risks could be given. There would appear to be a need for classification of early onset nystagmus within the first few years of schooling. Decisions on education, and appropriate measures such as aids to low vision glasses,⁴ could be introduced at an early age.

The probability that complete congenital achromatopsia is more common than has been previously suggested is a further indication that all children with early onset nystagmus should be investigated more thoroughly, particularly with the ERG.

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Retinal sensitivity in hereditary retinal degeneration in Abyssinian cats: electrophysiological similarities between man and cat

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SUMMARY The functional and electrophysiological similarities in the changes in the electroretinogram (ERG) of man and cat affected by hereditary retinal degenerative disease were studied. The results of a series of log intensity-amplitude studies in a group of young affected Abyssinian cats were fitted to the Naka-Rushton relationship by means of a mathematical package on the University of London mainframe. The analysis showed that the amplitude of the maximum dark-adapted b-wave was significantly reduced by the end of the period studied but that the value of k , a variable inversely equivalent to retinal sensitivity, was only slightly reduced by the retinal degenerative process. The electrophysiological findings thus are similar to those found in cases of human diffuse dominantly inherited retinitis pigmentosa.

A recessively inherited rod-cone degeneration has been described in a strain of Abyssinian cats.^{1,2} Often at the age of 1.5 to 2 years the fundus is ophthalmoscopically normal, but the end stage (blindness) occurs after another 3–4 years. Thus the progression of the disease is rather slow.

Previous electrophysiological as well as ultrastructural investigations in clinically affected adult cats^{3,4} have shown that the photoreceptors are primarily affected in the disease, the rod system being affected prior to that of the cones. A significant reduction of scotopic a- and b-wave maximum amplitudes is seen at an early stage when only minor changes are observed by ophthalmoscopy. At this time there is no significant reduction of the c-wave amplitudes in comparison with controls, and SP recordings and 30 Hz flicker responses are normal.

One of the aims of investigating photoreceptor degenerations in animals is to obtain models for similar diseases in humans. Several rodent^{5,6} and canine^{10,11} retinal dystrophies have been well documented. But it is still uncertain whether these diseases are closely related to any human form of retinitis pigmentosa (RP). This is true also for the Abyssinian cat retinal degenerative disease, though

several clinical and morphological similarities between the diseases in cat and human are seen.^{2,4} This paper is concerned with the functional and electrophysiological similarities in the changes of the electroretinogram (ERG) of man and cat affected by hereditary retinal disease.

Material and methods

ERGs were obtained in 10 affected and 11 control cats. The methods have been described in detail elsewhere.¹² In brief, general anaesthesia was induced with sodium thiopentone and maintained with halothane; the pupils were dilated with atropine and neosynephrine. The silver-silver chloride corneal electrode was contained in a diffusing contact lens, which helped to make retinal illumination uniform. The animals were dark adapted for 45 minutes, after which the series of ERGs were obtained. The 20 ms white light flashes were produced by an electronic shutter and delivered to the eye with a fibre optic system placed in the visual axis. Intensity was varied over a range of 5 log units by inserting neutral density filters in the light path. The maximum light intensity employed was 85 000 lux, measured at the surface of the contact lens. The amplifier bandpass was 0.3 to 1000 Hz. Responses were displayed and photo-

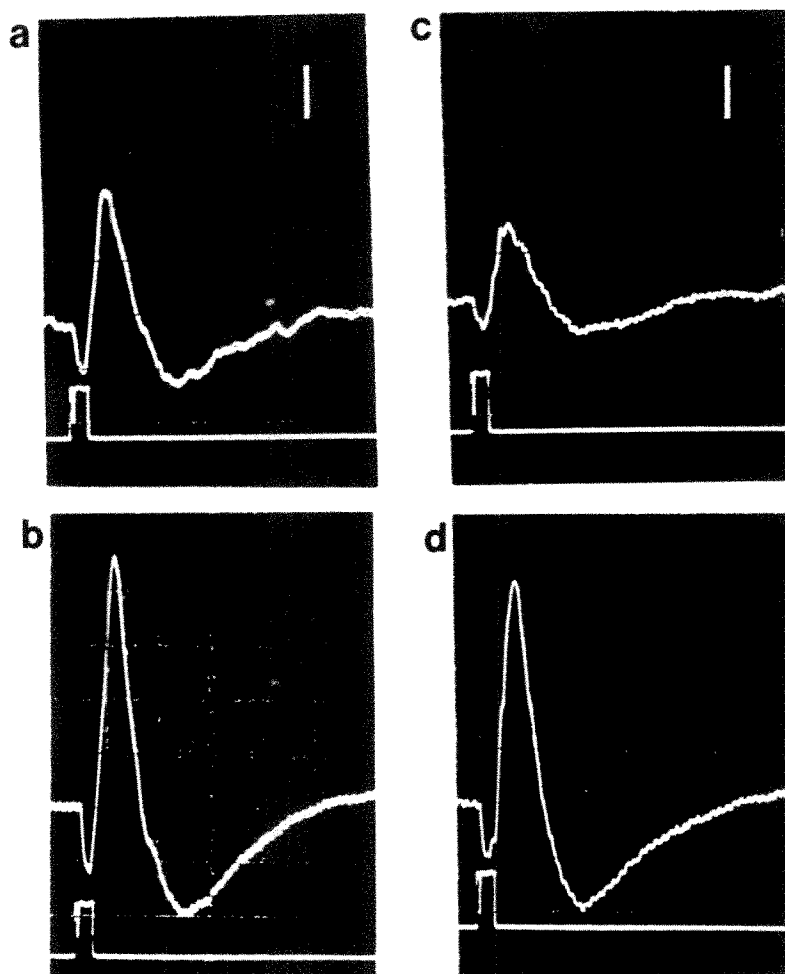


Fig. 1 Representative ERGs of (a) a 13-week-old Abyssinian kitten homozygous for hereditary retinal degeneration (affected); (b) a 12-week-old control kitten; (c) a 56-week-old affected Abyssinian; and (d) a 56-week-old control cat. Vertical bar for (a) and (b) = 100 μ V, for (c) and (d) = 50 μ V. 20 ms of white light stimulus (31 000 lux) indicated.

graphed from the screen of a storage oscilloscope. The first records were obtained at 8 weeks of age. The animals recovered from the anaesthesia and the test was repeated in several animals at intervals up to 104 weeks of age.

Results

Representative recordings are shown in Fig. 1. As already shown,¹² there is no change in ERG wave form or implicit time, but the magnitude of the a- and b-waves is decreased in affected animals.

In the youngest age group (group 1; 8–16 weeks) there was a significant decrease in the maximum dark adapted b-wave amplitude but not of the corresponding a-wave amplitude when affected cats were compared with controls. In group 2 (17–32 weeks) the a- and b-wave decreases observed were not statistically significant, probably because during this

time period both the normal and the affected ERG amplitudes become reduced as the kittens' retina matures.^{13–15} In group 3 (33–104 weeks) both a- and b-wave maximum amplitudes were significantly reduced. The quantity of light required to elicit a criterion voltage (50 μ V) was determined, and for the youngest age groups there were no significant differences between affected and controls. In group 3 there was in one animal an increase in the light intensity required to elicit a criterion voltage b-wave.

To investigate this point in more detail we fitted the results to the Naka-Rushton relationship,¹⁶

$$V = V_{\max} \frac{I^n}{I^n + k^n}$$

where V is the response amplitude in μ V, $V_{\max}$ is the maximum ERG amplitude, I is the stimulus luminance, k represents the light intensity required to produce a half-maximal response, and n is a

dimensionless constant that determines the slope of the function.

The best fitting results (least squares method) were obtained by an iterative procedure using the mathematical package on the University of London mainframe. Results were obtained for the normalised results of all the animals in each group, and are shown in Table 1. The variation in the size of $V_{\max}$ was as in the previous study.¹² Note that the computer prediction of the maximum b-wave amplitude was only 3–4% larger than obtained in the experiment. The values of k varied slightly from group to group.

After the age of 17 weeks the value of k for the affected groups was significantly less than for the normal control kittens. The value of n was similar for all groups, but was calculated to be considerably less than unity. Fig. 2 shows representative graphs of results from individual animals. It can be seen that the calculated functions fit the results reasonably well and that there is a real difference in the constants calculated by the computer program.

An attempt was made to analyse the a-wave data in the same way as we have analysed the b-wave data, but the computer program was unable to converge on a unique relationship.

Discussion

This analysis has shown that the amplitude of the maximum dark adapted b-wave is reduced by the end of the period studied and that the value of k , a variable inversely equivalent to retinal sensitivity, has been slightly reduced by the retinal degenerative process. The electrophysiological findings thus are similar to those found in cases of human diffuse dominantly inherited retinitis pigmentosa,^{17,18} in which large rod ERGs are seen, and the value of k is only slightly affected. In patients with such disease the visual fields are often sizeable, and large areas of retina are found with well preserved scotopic

function, so that rod threshold is not raised significantly.

However, in man there are very few reports on retinal ultrastructure in dominant disease^{19–21} and none at all which relate to the state of the retina at an early stage of the disease, when vision is only scarcely affected. Such information is available for these cats (Narfström K, Nilsson SE, in press).

Electron microscopy showed that in this strain of Abyssinian cats retinal alterations may be found in affected kittens already before the time of retinal maturation.²² In kittens aged 9 to 84 days homozygous for the defect, but still with an apparently normal retina as judged by ophthalmoscopy, there are a certain number of rod outer segments, usually less than 50% but occasionally more, that appear completely disorganised and some even disrupted. These lesions are found in a patchy distribution over the retina, and are often more frequently observed in the peripheral retina than the central parts.

It is of interest to consider whether this histological picture can be reconciled with the electrophysiological and densitometric findings in man and cat as well as with psychophysical findings in man.

If sensitivity is only slightly reduced when a considerable number of rod outer limbs are disorganised or disrupted, this is in keeping with the idea that in many cases of RP sensitivity is reduced only to the extent that the light-absorbing power of the retina is reduced—that is, its 'quantum catch'.^{17,23} Thus, if 50% of rods are affected, sensitivity would be reduced only by 0.3 log unit. In man and in cat^{24,25} rhodospin content and sensitivity reductions which obey this relationship have been reported.

Implicit, on this view, is the assumption that affected rods do not influence the ERG b-wave in any way: they behave as though they were absent. This need not be the case. It is possible that even if the transduction mechanisms of affected rods are abnormal the dark current is present (and light

Table 1 Pertinent results for the ERG a- and b-waves for groups 1, 2, and 3. C=controls cats. A=affected cats

b-Wave	Group					
	1		2		3	
	C	A	C	A	C	A
$V_{\max}$ normalised	1.04	1.03	1.03	1.04	1.02	1.03
$V_{\max}$ V (SD)	988.0 (124.0)	581.0 (13.8)	450.5 (34.0)	299.3 (27.8)	324.5 (20.9)	188.0 (16.9)
log k	2.97 (0.06)	2.78 (0.07)	3.21 (0.07)	2.47 (0.06)	3.13 (0.06)	2.75 (0.08)
n	0.43	0.49	0.52	0.49	0.45	0.45
a-wave	1		2		3	
	C	A	C	A	C	A
$V_{\max}$ V (SD)	208.0 (35.6)	163.3 (21.4)	110.8 (23.8)	70.8 (13.1)	89.0 (43.9)	52.1 (10.5)

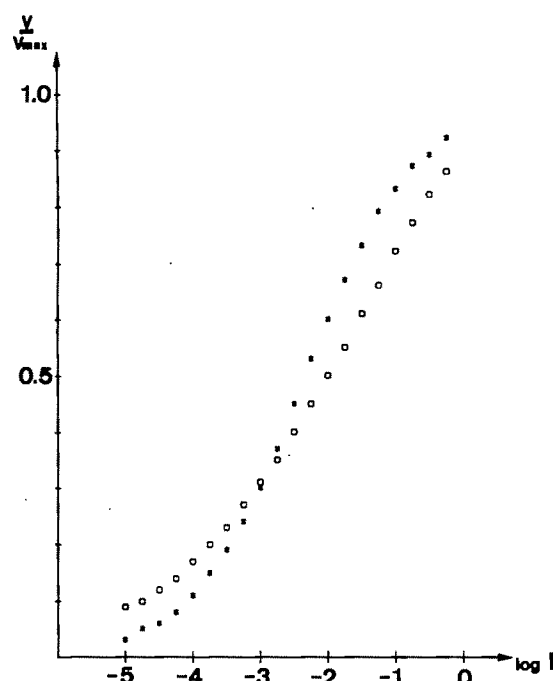


Fig. 2a

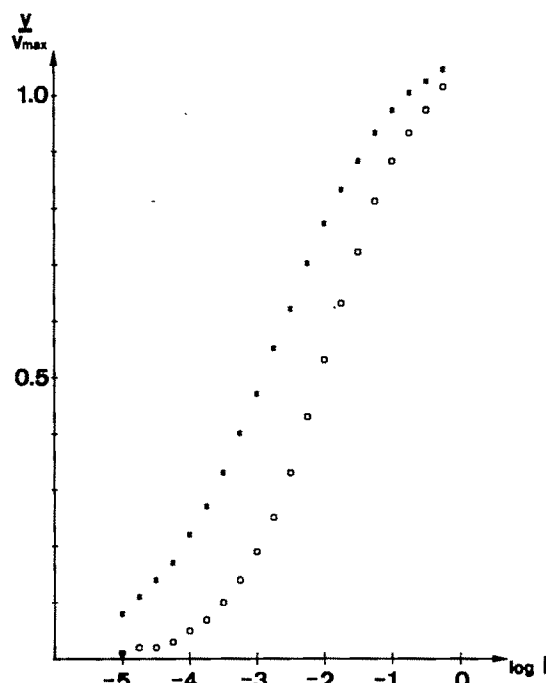


Fig. 2b

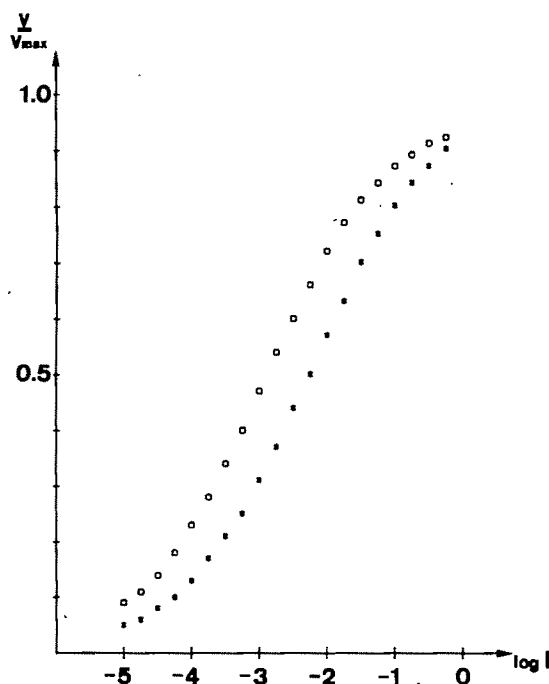


Fig. 2c

Fig. 2 Intensity-amplitude relation obtained from an affected and a control cat in each group in order to illustrate the theoretical fitting of results done by the computer. (a) Group 1: 8-16 weeks. (b) Group 2: 17-32 weeks. (c) Group 3: 33-104 weeks. Circles=normal cat, stars=affected Abyssinian cat.

cannot change it), so that a constant output of neurotransmitter occurs from the affected rod presynaptic terminals. Alternatively the membrane of the disorganised rod might be generally permeable but all specific ion channels and neurotransmitter channels absent. In such a case, if rods remain electrically interconnected,²⁶ when the responsive rods absorb light, the reduction in dark current would cause the cell to have to charge up a larger area of the cell membrane than in the normal eye.

What is common to all these possibilities is that the degeneration has two separate effects. If quanta fall on 'affected' rods, they are not absorbed—for the rods have vanished—or produce no excitation. Therefore sensitivity is reduced to an extent determined by the loss of rhodopsin, or by the reduction in the number of normal rods. If the quanta are absorbed in 'unaffected rods', the transduction mechanisms produce a normal electrical signal in the

outer limb, but this signal is then 'diluted' because of the presence of the abnormal rods and produces a reduced effect at the rod synapse. The value of k would increase to a greater degree than expected from counts of the number of rods lost. In addition, the linear part of the $V/\log I$ curve would extend to higher light levels in the affected animals, so the proportion of $V_{\max}$ elicited by the most intense light and the value of n should change. This does not occur, and therefore the results support the view that, once a rod has become affected with the disorganisation shown, it ceases to exert any influence on signal transmission. In humans clinical psychophysical studies as well as electroretinography, field tests, and dark adapted perimetry have independently led to the suggestion that a drop out of individual rods occurs.^{17 18 23 27}

In both man and cat the maximum b-wave is reduced. In man this reduction is related to the decrease in the area of functioning retina, as defined by perimetry. In cats of the ages we investigated there are no large areas where all rods are lost. Because the bipolar cells integrate rod activity over a relatively large area, a loss of only a proportion of their input which reduces sensitivity should not reduce the number of b-wave generators, and thus, unless some other factor intervenes, $V_{\max}$ should remain unchanged. It is known that the b-wave is produced by Müller cells. One possibility is that all the cells of a group which are invested by a particular Müller cell become inactive at the same time. Alternatively, the reduction in the number of rods alters the environment of the Müller cell and stops it generating a maximal current.

The clinical and laboratory findings in the retinal degenerative disease in this strain of Abyssinian cats shows that it is distinct from other reported RP-like diseases in dogs and rodents. The very slow time course of the degeneration and the fact that a reduction in ERG amplitudes occurs without major loss of retinal sensitivity is thus remarkably similar to the findings in some types of human disease.²⁸ Specifically, in dominantly inherited human RP¹⁷ the value of k is somewhat increased, with a reduced maximum b-wave amplitude, in just the same way as in affected Abyssinian kittens.

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Dynamic nature of posterior subcapsular cataract

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SUMMARY Posterior subcapsular cataracts were studied in 10 patients (19 eyes) and were photographed at four to 12 weeks intervals by the Oxford Retroillumination Camera. Changes in the fine structure of PSC may occur in as short a time as four weeks. Posterior subcapsular cataracts are shown to be in a state of flux and are not, as might be assumed, slowly but relentlessly progressive. This could imply the existence of a repair mechanism in the lens.

Posterior subcapsular cataract (PSC) in the absence of any other form of lens opacities is relatively uncommon. In the Framingham Study isolated PSC occurred in 2.1% of a population aged 52 to 85 years old.¹ PSC occur in a wide variety of conditions. Eshagian lists 38 associations.² Its histopathology has been well described.^{3,5} Quantitative microradiography has demonstrated marked shifts in protein concentration at the junction of normal lens fibres and PSC, creating scattering interfaces.⁶ PSC have been studied by the Scheimpflug slit-image camera. Lenses with PSC have been shown to be smaller than normal and to be associated with a small or absent anterior clear zone.⁷

However, there does not exist to our knowledge any study of the fine morphological changes that might occur with time in PSC. The present study was designed to study changes with time in their fine morphology. Lenses with PSC were photographed by the prototype Oxford retroillumination camera after full pupillary dilatation.^{8,9}

Material and methods

APPARATUS

Fincham¹⁰ described a method of photographing opacities of the ocular media by retroillumination photography. His apparatus was mounted on a slit-lamp and was provided with a deep orange filter (Ilford Micro 5) in order to increase the contrast on black-and-white film.

In 1980 Kawara and Obazawa¹¹ improved on Fincham's system. A pair of cross polarisers was used

to minimise the corneal reflection. A fixation light was placed in front of the eye which was not being photographed. They found that the position of maximum retroillumination occurred when the optic disc, acting as a reflector, lay in the illuminating beam. Repeatability is sometimes difficult with this method.

Brown and colleagues have described the Oxford retroillumination camera.^{8,9} It has two features of note. First a neutral density standard is incorporated into the system to allow, by image analysing techniques, comparison of density changes occurring in sequential photographs. Second, it has fixed fixation lights placed in front of the eye being photographed. These fixation lights are offset by 15.5° horizontally and 1.5° vertically to the illuminating beam. In the average eye this brings the optic disc into the illuminating beam and thus automatically provides maximum retroillumination. This system of fixed fixation lights allows repeatability of results.

In this study the prototype Oxford retroillumination camera was used. It was mounted on a Zeiss photoslit lamp, and the Zeiss flash unit was used.

SELECTION OF PATIENTS

Ten patients with PSC only or PSC with a minimal degree of other cataract insufficient to interfere with photography of the PSC were selected from patients attending the Clinical Cataract Research Unit in Oxford. No patients were diabetic. They had either age related PSC (three patients) or had undergone renal transplantation (five patients) or total body irradiation prior to bone marrow transplantation in the past (two patients). There were 19 eyes in total. The mean age of patients was 60 years, range 25 to 79 years.

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Fig. 1a Subtraction photograph of Fig. 1b and Fig. 1c.

METHOD

The pupils were dilated with phenylephrine 10% drops and tropicamide 1% drops in order to obtain a pupil diameter of 7 to 8 mm. The lenses were graded by the Oxford Clinical Cataract Classification

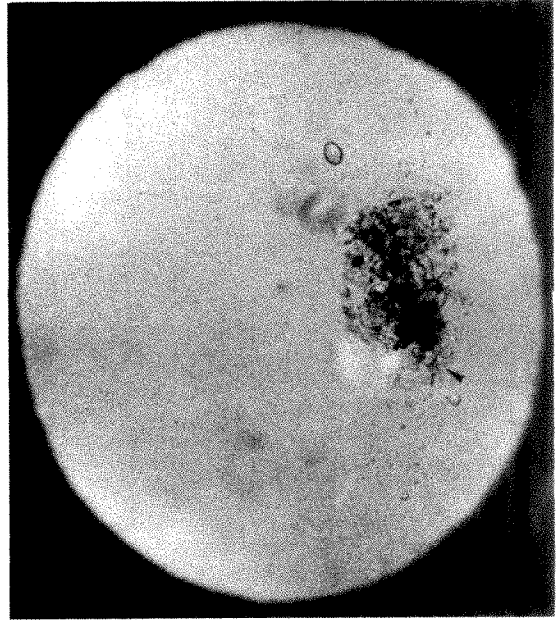


Fig. 1c Retroillumination photograph of same eye as Fig. 1b photographed six weeks later.

System.¹² This is a slit-lamp based, in-vivo system. Posterior subcapsular cataracts in this system are graded according to diameter: grade 0 represents no PSC and grade 5 a PSC occupying 81% to 100% of an 8 mm diameter pupil. This classification of PSC has a weighted kappa value of 0.81 and 0.86 inter- and

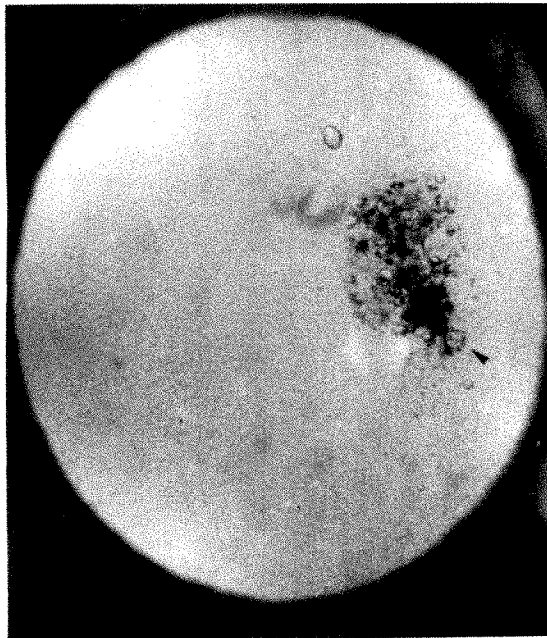


Fig. 1b Retroillumination photograph.

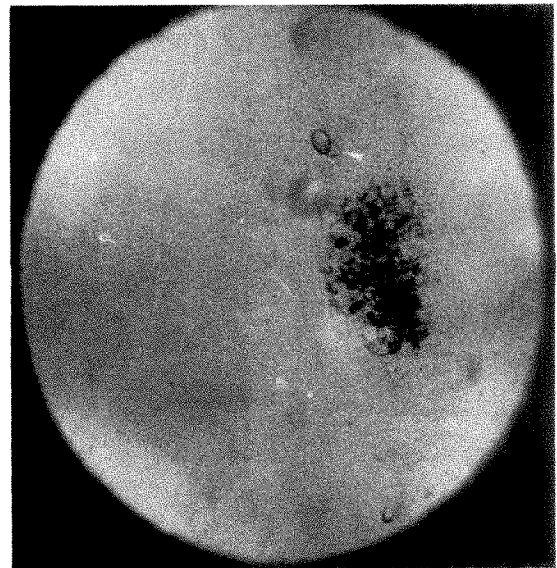


Fig. 1d Retroillumination photograph of same eye as Fig. 1b photographed eight weeks after Fig. 1c.

intraobserver variation respectively.¹³ In this study one eye was grade 1, six eyes were grade 2, 10 eyes were grade 3, and two eyes were grade 4.

The Oxford Retroillumination Camera was focused on the PSC. They were photographed again at intervals of four to 14 weeks. The mean interval was 10 weeks. Four patients were photographed on two occasions, five on three occasions, and one on four occasions.

Sequential pairs of negatives of PSC taken of the same eye at different time intervals were projected at 20 times magnification on a grid. Each square in the grid was examined, and the number of vacuoles which had disappeared completely and the number of new vacuoles were counted. Only vacuoles greater than 50 μm were counted.

As no account was taken of vacuoles which had changed in size or shape in the part of the study described in the preceding paragraph, an attempt was made to analyse morphological changes within the PSC by subtraction photography. Ten pairs of negatives were examined by the technique of subtraction photography. In practice it was difficult to obtain exact superimposition of the pairs. Thus subtraction photography was of value only as a guide to areas of maximum change. The original set of negatives was always examined in order to confirm that the changes suggested by the subtraction were not artefactual. Subtraction photography was found to be useful only for illustrative purposes. Computerised image analysis may allow objective quantification of changes in PSC in future.

Results

In all cases changes in the fine structure of PSC were seen. Vacuoles could be identified which appeared and disappeared with time. On average four new vacuoles appeared and three old vacuoles disappeared per month. The range was one to six. There were not enough pairs to draw any statistically significant conclusions, but it seemed that the rate of change was not related to the size of the PSC. However, it would seem that the more vacuolated the PSC the greater the rate of change as defined in the preceding section.

Fig. 1a is a subtraction photo of a pair of photographs (Figs. 1b and 1c) taken at a six-week interval. It suggests that the area of maximal change was at the inferior tip of the triangular shaped PSC indicated by the large white arrowhead. The vacuoles indicated by the small white arrowhead have been correctly superimposed. The vacuole with the small white arrow has a dark shadow to its left suggesting that there might have been a small shift of one of the subtraction pairs relative to the other. However, the complex with the large white arrow has its dark shadow to its right, and this militates against any shift having occurred. This is thus an example of an acceptable superimposition of negatives. Figs. 1b and 1c are the original pair from which the subtraction picture was taken. It is to be noted that the vacuoles (arrowed) at the inferior tip of the PSC have changed. This change has occurred in six weeks. The surrounding features are similarly in focus in the two

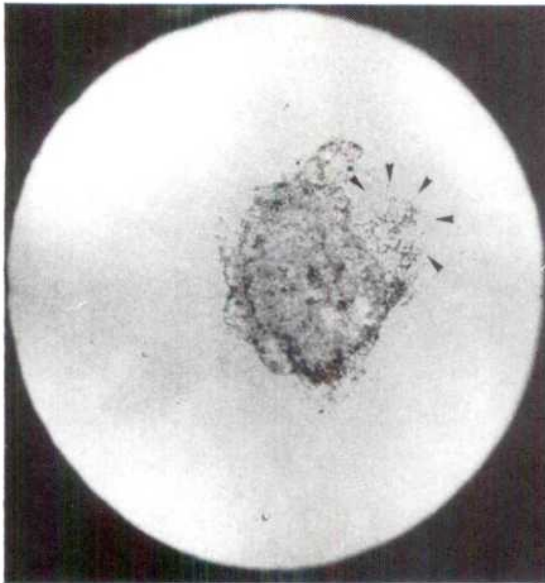


Fig. 2a Retroillumination photograph taken June 1987.

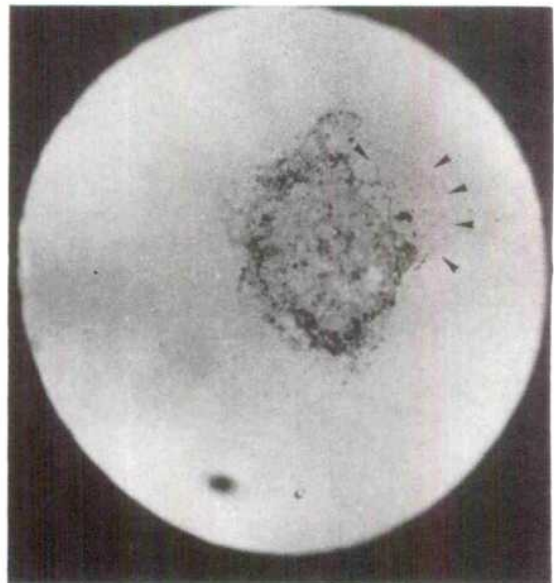


Fig. 2b Retroillumination photograph of same eye as Fig. 2a taken July 1987.

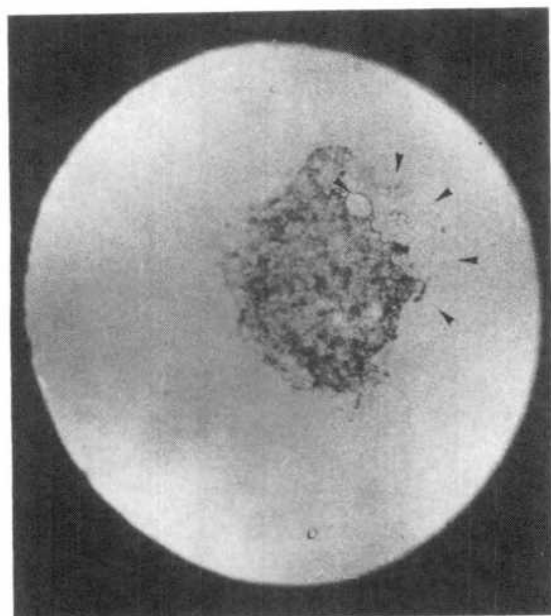


Fig. 2c Retroillumination photograph of same eye as Fig. 2a taken August 1987.

photographs, showing that the changes occurring are not an artefact caused by differing plane of focus. Fig. 1d was taken eight weeks later. The appearance of a new vacuole is indicated by the white arrow.

Figs. 2a, b, and c are from the same eye taken in June, July, and August. The area arrowed in Fig. 2a shows the vacuoles which make up the structure of the PSC. Within the short space of one month these vacuoles start to break up and disappear as shown in Fig. 2b. A new, optically denser and solid-looking structure appears. Fig. 2c shows the situation a further month later. The dense opacity has increased in size and there is further break-up of the vacuolar structure of the PSC. The diameter of the larger vacuoles is about 300 μ m.

POSSIBLE SOURCES OF ERROR

Fixation loss. This is a potential source of error. The camera back used has a graticule incorporated which consists of a circle and crosshairs. There is a small corneal reflex seen during photography which is due to the reflection of light from the fixation light. When this reflex is aligned with the centre of the circle, fixation is central. In spite of this there may be an occasional fixation loss, and therefore the effect of fixation loss of the fine morphology of PSC was studied. Photographs were taken on axis and with the eye deliberately off axis by 15.5°. A 5° fixation loss is readily noticed by the photographer. The negatives were compared at 20 times magnification. Six PSC

were thus studied. There was no change in the number of vacuoles seen in the PSC. Fixation loss is therefore not a significant problem in the study of qualitative changes in PSC.

Variation in the plane of focus. As the constituents of the PSC are three-dimensional structures it is possible to induce artefactual changes in photographs by focusing at different planes. To guard against this, common features in a sequential series of photographs must be clearly identified and found to be similarly in focus before it can be said that definite change has occurred.

Repeatability of photographs. To assess the repeatability of the method retroillumination photographs of PSC were taken at separate sessions and the negatives compared.

Patients were selected on the criteria used in the dynamic nature of PSC study. The pupils of five patients (10 eyes) with PSC were dilated with phenylephrine 10% drops and tropicamide 1% drops to obtain a pupil diameter of 7 to 8 mm.

Photographs were taken with the camera accurately focused on the PSC. The PSC was rephotographed between one and 24 hours later. To assess the repeatability of the method a masked observer was shown pairs of negatives projected on to a screen at a final magnification of 90 times. The pairs were of two types. There were 10 pairs of photographs taken as described above and 10 pairs in which the same eye with a PSC had been photographed at four to 12 weeks' interval. The order of presentation was randomised. The masked observer was asked to decide whether a pair of photographs was identical (and therefore taken at an interval of one to 24 hours) or whether there was any difference between the two photographs being projected. A difference was defined as either the appearance or disappearance of a vacuole, or a change in shape of the vacuole. A diagram was made of the changes seen so that the results could be verified later.

The observer was able to identify the appearance or disappearance of vacuoles in the 10 pairs of negatives taken at an interval of four to 10 weeks. There were also differences in the size and shape of vacuoles noted. But he was unable to identify any difference in any of the 10 pairs taken at one to 24 hours. The retroillumination camera thus has a degree of repeatability sufficient for this study.

Figs. 3a and 3b were taken at a one-hour interval and illustrate the high degree of repeatability which may be obtained with the Oxford retroillumination camera.

Discussion

Posterior subcapsular cataracts are demonstrably in a

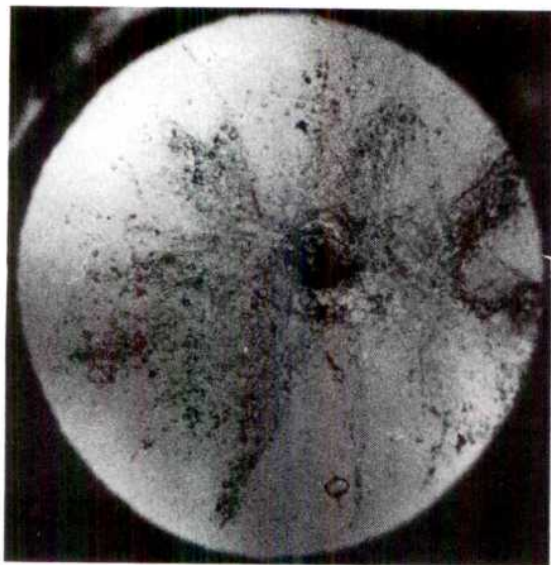


Fig. 3a Retroillumination photograph.

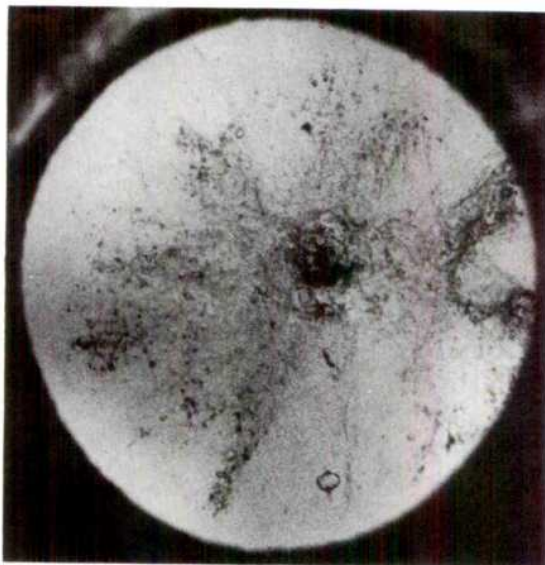


Fig. 3b Retroillumination photograph of same eye as Fig. 3a taken one hour later.

state of flux. Vacuoles appear and disappear continually. Sometimes they are replaced by a denser opacity.

Ultrastructural studies have suggested that the evolution of PSC is associated with fibre swelling and breakdown.⁴ In lenses with posterior subcapsular cataract a sequence has been suggested of increased or altered interdigitation of fibres, nipping off of interdigitating processes, fibre swelling, formation of intercellular and interfibre lakes and vacuoles, and total fibre breakdown.^{6,14,15} Fibre breakdown is accompanied by the formation of complex and bizarre membrane figures such as 'figure of 8' patterns and 'tramline' figures.¹⁴ Eshagian has shown that epithelial cells have prominent, rough, endoplasmic reticulum and a Golgi apparatus as they move from the equator towards the posterior pole. He concludes that this represents an increase in cell metabolic activity. Extracellular granular and fibrillary material are produced.⁵ Within this evolutionary progress could lie the explanation for the changes in density and morphology of the figures documented photographically in PSC.

Repair processes in the lens are not well recognised. We have proposed that the lens has an uncoupling mechanism which responds to injury or damage by ionically disconnecting damaged fibres from undamaged ones. This implies closure of the gap junctions which connect neighbouring fibres electrically and ionically. Furthermore it is suggested that an annealing mechanism could exist in which a part of a damaged fibre was sealed off from the rest of the fibre.¹⁶ A process might thus occur by which focal

lens opacities were compartmentalised before the whole lens fibre was involved. Vrensen and Willekens have electron-micrographic evidence for this.¹⁷ They have shown a clear demarcation line running across lens fibres and separating normal from cataractous segments. It is thought that in senile PSC the secondary migration of the lens epithelial cells may be a response to primary damage at the posterior pole of the lens and represent attempts at repair.²

Though the findings in this study that features appear and disappear could be simply explained on the basis of the evolution of cataract, they could also in part represent the occurrence of a reparative process.

CONCLUSIONS

These findings may have some relevance to our expectations for the medical treatment of cataract. The majority of cataracts are age related or 'senile' cataract. A number of potential drugs for the treatment of cataract have been proposed in recent years.^{18,19} It is likely that their use in the treatment of senile cataract will be directed to the prevention of progression in those with established lens opacities. There will be some interest in the possibility of reversing existing opacity. The dynamic features of cataract observed in this study offer some hope that this may be possible.

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Presumed ocular histoplasmosis syndrome and linear streak lesions

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SUMMARY Five cases of subretinal neovascular membranes in the macula associated with punched out chorioretinal scars and linear streaks were seen in five Dutch patients. Clinically the fundus lesions are consistent with those of presumed ocular histoplasmosis syndrome (POHS) seen in the United States of America. Cutaneous serological testing for histoplasmin reactivity was negative in the three patients tested. Of special interest is the presence of linear streaks in association with POHS. They have not been previously described in patients from Europe with this syndrome.

Although the association of haemorrhagic macular lesions and histoplasmosis was noted as early as 1942,¹ the syndrome of presumed ocular histoplasmosis (POHS) was not defined until 1959 by Woods and Wahlen.² Their description of disciform lesions at the macula accompanied by multiple peripheral, discrete atrophic lesions was expanded to include peripapillary pigment epithelial atrophy³ and the absence of aqueous and vitreous inflammation.⁴ A fourth sign of linear peripheral streak lesions was eventually added to the common triad of POHS.^{5,6}

POHS is a common disease in the United States of America, carrying a risk of bilateral loss of central vision.⁶ In Europe the syndrome is not so common and was mostly reported as being associated with negative histoplasmin reactivity.⁷⁻¹¹

Thus an acute haemorrhagic maculopathy very similar to the disciform reaction of the POHS, with or without peripapillary and peripheral changes has often been described by European authors under a variety of names.¹⁰⁻¹⁶

We present five cases of POHS seen at the Institute of Ophthalmology of the University of Nijmegen, with equatorial linear streak lesions as an interesting additional finding.

Case reports

CASE 1

A 42-year-old man presented in 1979 with a complaint of metamorphopsia in his right eye. Best

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corrected visual acuity was 6/75 in the right eye and 6/6 in the left eye, with a myopic refraction. On ocular examination the media were clear, with no evidence of inflammation.

Fluorescein angiography of the right fundus disclosed subretinal neovascularisation in the macula, with histoplasma spots in the perifoveal area and inferior to the disc. At the equator, temporally and inferotemporally, linear streaks one to two disc diameters in width and parallel to the ora serrata, showed window defects, with occasional blockage of fluorescence corresponding to spots of hyperpigmentation. Similar lesions were seen in the left fundus (Fig. 1).

A histoplasmin skin test was negative. Spontaneous resolution of the former subretinal neovascular membrane with subsequent recurrences occurred during the seven-year follow up, leading eventually in the right eye to a visual acuity of 6/60 and a dry scar.

CASE 2

This 22-year-old woman presented in 1982 with a sudden decrease in her left central vision. Her visual acuity was 6/6 in the right eye and 6/400 in the left (emmetropic refraction). The media were clear, without evidence of inflammation.

Fluorescein angiography of the left eye revealed a subretinal neovascularisation inferonasal to the fovea. Either hyper- or hypofluorescent linear streaks according to the amount of pigment were seen in the equatorial area throughout the entire circumference of the globe. Posterior to the streaks

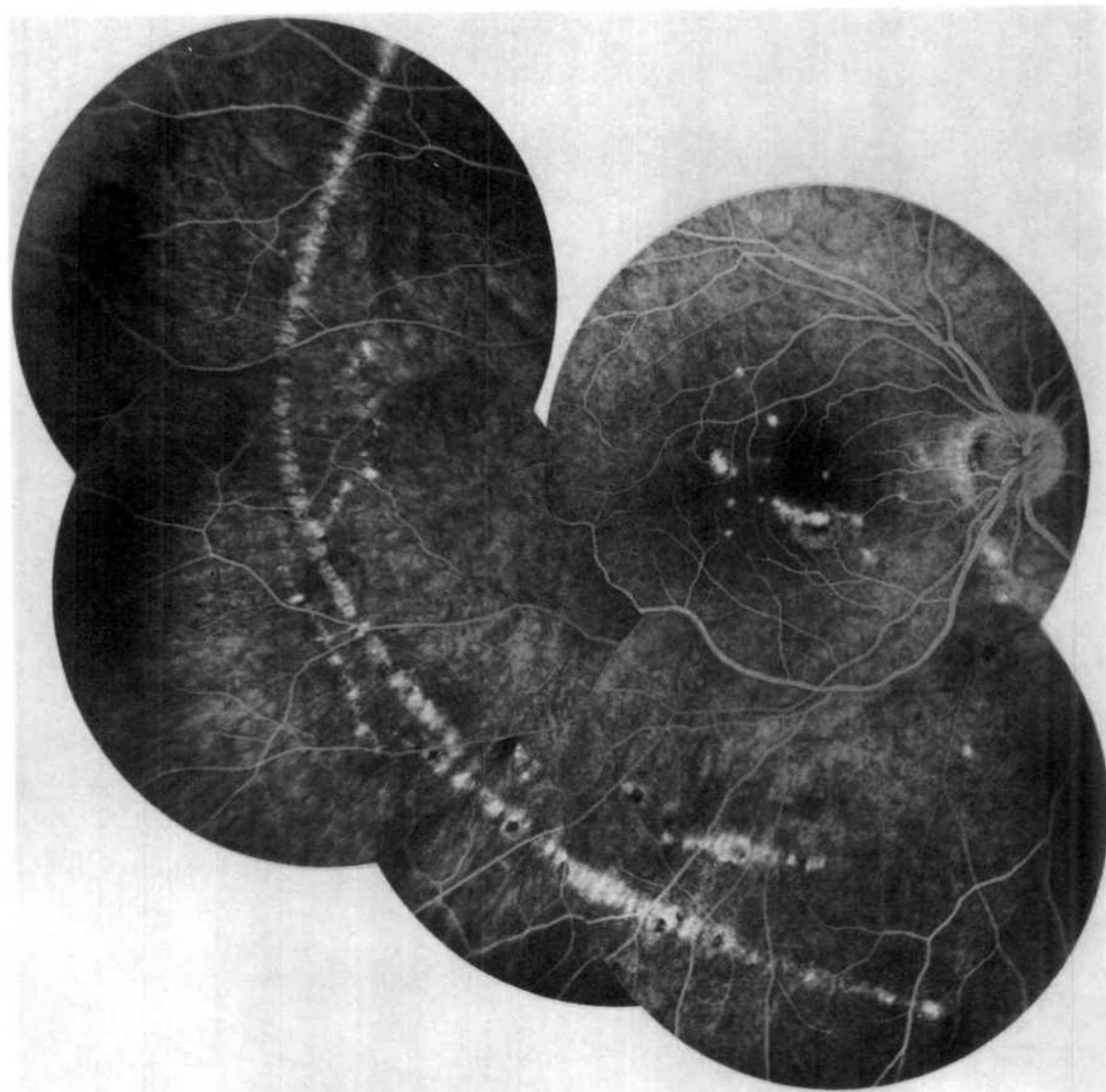


Fig 1 Case 1 (A) Fluorescein angiogram of the right fundus.

were a few histoplasma spots in the periphery of the inferior quadrants (Fig. 2).

A histoplasmin skin test was negative. Complete obliteration of the subretinal neovascular membrane was achieved with krypton laser photocoagulation, leading to a 6/6 visual acuity in the left eye at a five-year follow-up.

CASE 3

This 49-year-old man, already diagnosed as having POHS in the right eye, presented at our institute in 1985 complaining of a two-week loss of vision in his

left eye. Corrected vision was 6/15 in both eyes with a myopic refraction. No evidence of ocular inflammation was detected.

On ophthalmoscopy the right eye showed a dry scar in the macula, histoplasma spots scattered either throughout the periphery or the posterior pole, and a linear streak inferotemporally. The left eye had a juxtafoveal neovascular membrane with linear streaks at the equator, inferiorly and inferotemporally. Posterior and anterior to the streaks were a few histoplasma spots (Fig. 3).

Tests for histoplasmosis were negative. At follow-

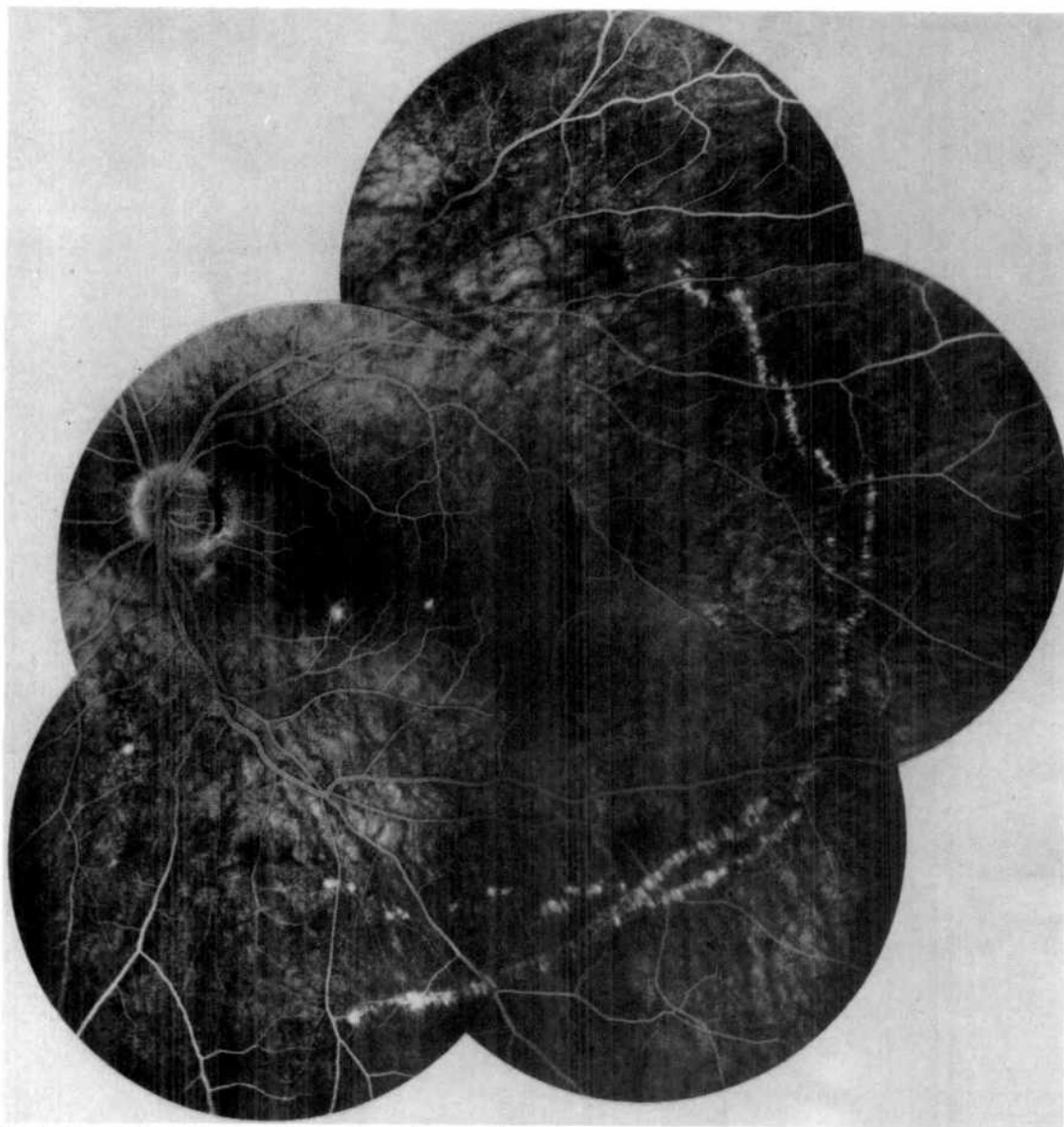


Fig 1 Case 1 (B) same patient, fluorescein angiogram of the left eye.

up, still in progress, the patient showed a marked improvement in the corrected visual acuity in the left eye to 6/75, with a spontaneous involution of the subretinal neovascular membrane.

CASE 4

This 20-year-old woman presented first in 1982 complaining of loss of vision in her left eye. Corrected vision was 6/6 in the right eye and 6/21 in the left eye

with a myopic refraction. The media were clear, with no evidence of inflammation in either eye.

Fluorescein angiography revealed a subfoveal neovascular membrane as well as histoplasma spots in the left eye and peripapillary atrophy with the presence of a chorioretinal scar in the superior temporal quadrant in the right eye.

In 1985 she returned with a two-week history of loss of vision in the right eye. Corrected visual acuity

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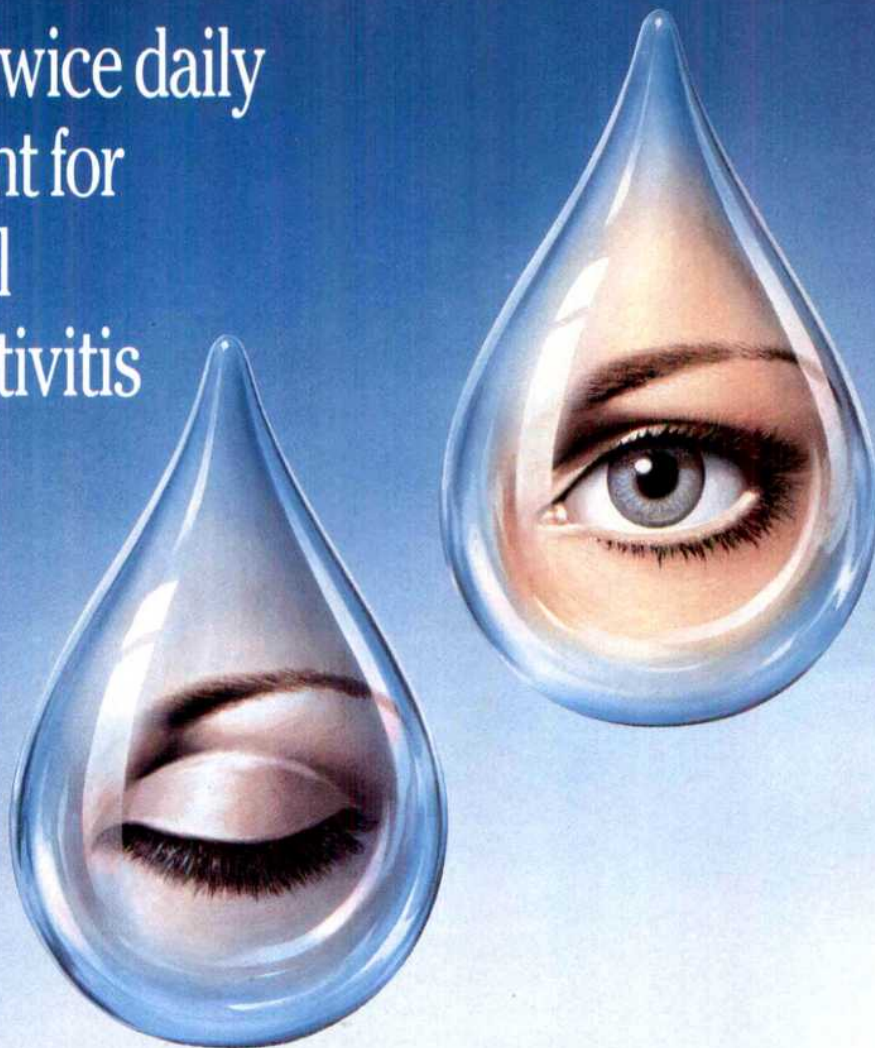
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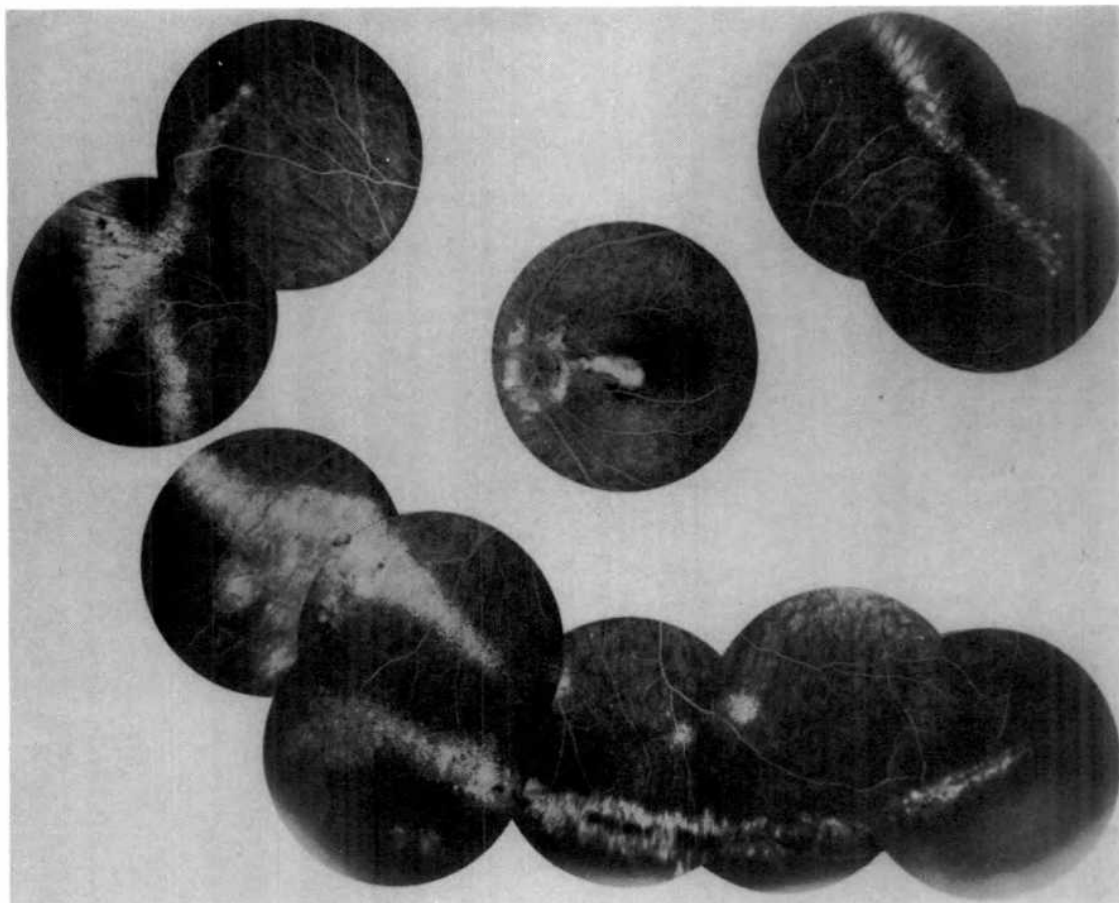


Fig 2 Case 2 fluorescein angiogram of the left fundus.

was 6/30 in the right eye and 6/12 in the left eye. There was still no evidence of inflammation in either eye.

Fluorescein angiography of the right eye showed juxtafoveal and subfoveal neovascular membranes as well as macular histoplasma spots. In the left eye there was staining of the dry scar in the macula, with subretinal bands of metaplastic retinal pigment epithelium, histoplasma spots throughout the fundus, and hypofluorescent linear streaks temporally and inferotemporally in the equatorial area (Fig. 4).

Spontaneous obliteration of the choroidal neovascularisation occurred in the left eye during a five-year follow-up. The final corrected visual acuity was 6/30 in the right eye and 6/12 in the left eye.

CASE 5

In 1984 this 39-year-old man presented for a routine examination. The visual acuity was 6/6 in both eyes

with an emmetropic refraction. The media were clear, without evidence of inflammation bilaterally.

Fluorescein angiography showed both eyes hyperfluorescent histoplasma spots and linear streaks temporally and inferotemporally (Fig. 5).

Follow-up examinations have shown a steady state.

Discussion

While typical POHS is common in the USA, the actual syndrome may be rare in Europe. Cutaneous and serological testing for histoplasmin reactivity in European patients with similar clinical pictures have been entirely negative.⁷⁻¹¹ The incidence of positive results of histoplasmin skin tests in Europe is extremely low, ranging from 0 to 2%.¹⁷

Since the aetiological association between this ocular syndrome and *Histoplasma capsulatum* infec-

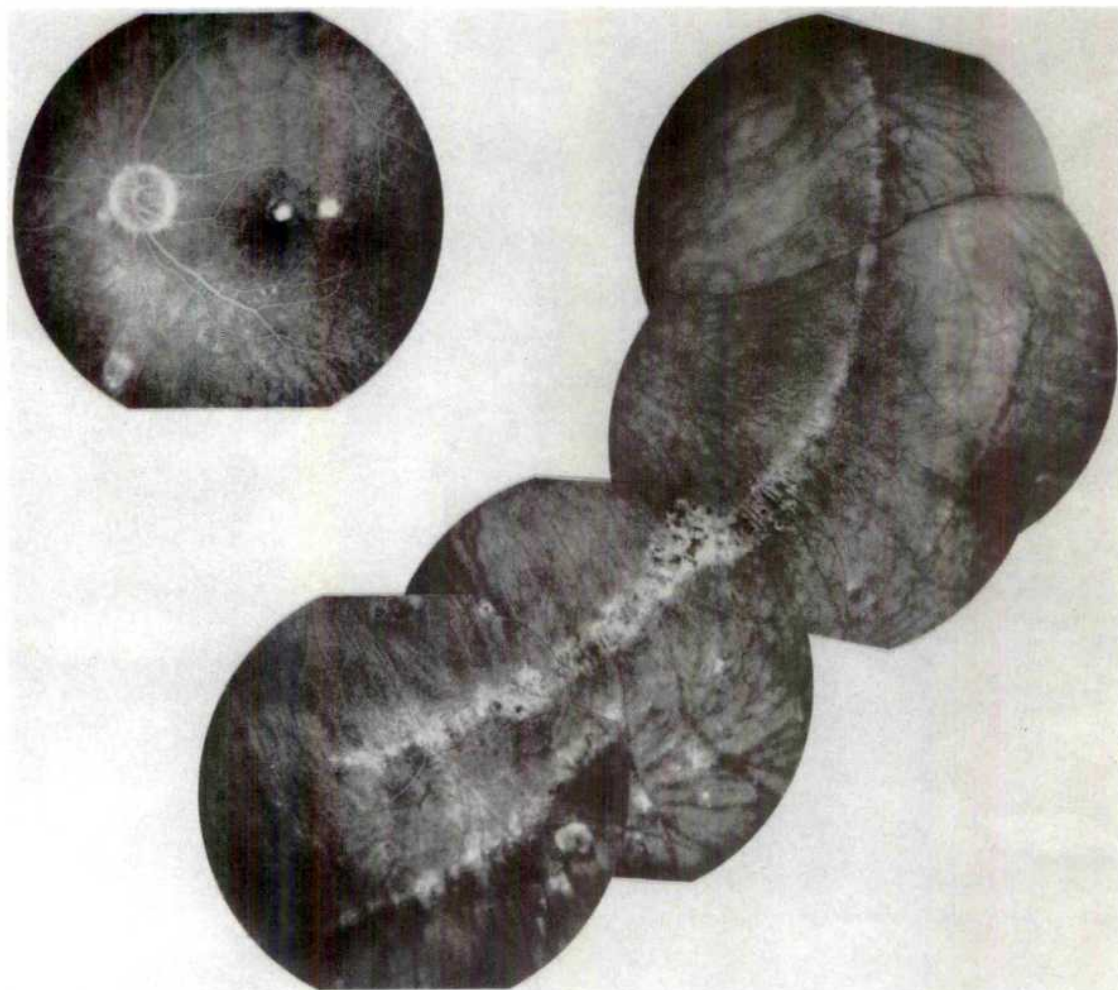


Fig 3 Case 3 fluorescein angiogram of the left eye.

tion rests solely on epidemiological data, and since these have not been entirely free of controversy,¹⁸ the diagnosis of POHS is based on the ophthalmoscopic finding of a neovascular lesion in the macula along with the presence of at least one atrophic scar—that is, histoplasma spot—in one or both eyes.¹⁹

Some of the cases described by European authors clinically resembled the POHS syndrome completely. Others did not, because an acute haemorrhagic maculopathy was the only sign described. The negative response to testing for histoplasmin reactivity was the reason these two groups were not diagnosed as presumed ocular histoplasmosis choroiditis. Thus they were seen as a single disease entity under various names.⁸⁻¹⁴

We agree with previous reports^{7,20-23} which indicated that it would be better to divide into two what was previously thought to be a single disease. In particular there are cases in young people where subretinal neovascularisation, at or near the fovea, resemble POHS, yet no other signs of POHS exist. These cases would have to be termed idiopathic and should be considered as a distinct group.

Our five cases show linear streaks associated with punched out chorioretinal scars (histoplasma spots) and haemorrhagic maculopathy in the absence of vitritis and anterior segment inflammation. A negative response to the histoplasmin skin test was found among the three tested cases. According to the Asbury rating system²⁴ four of our patients with

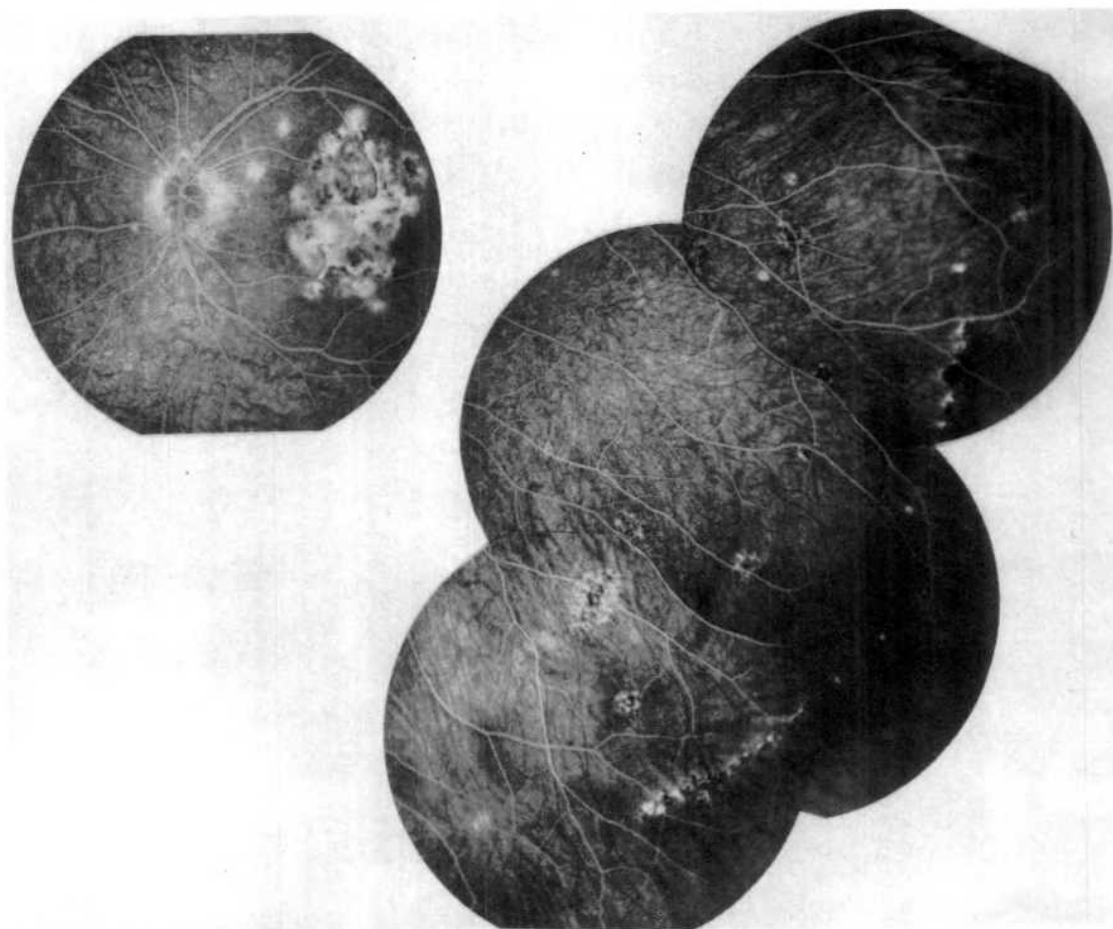


Fig 4 Case 4 fluorescein angiogram of the left eye.

streaks had an Asbury grade of four and one, case 2, of 3. High Asbury ratings (3 or 4) indicate typical POHS.

Two cases show some peculiarities. Case 5 has histoplasma spots and linear streaks bilaterally but no maculopathy. Case 4 was unilateral (left eye) at the first examination, with maculopathy and histoplasma spots only at the posterior pole of the left eye. Six months later the fellow eye was also involved (*de novo*), and the left eye showed a subretinal scar in the macula, an increased number of histoplasma spots scattered throughout the fundus, and linear streaks. This patient also had multiple lesions of the retinal pigment epithelium with recurrences similar to the ones originally described by Nozik and Dorsh²⁵ and subsequently by other authors,²⁶⁻²⁹ a condition recently termed 'recurrent multifocal choroiditis'. This entity is a retinal pigment epithelium and

choroidal inflammatory disorder characterised by multiple relapses and inflammatory signs in the vitreous and the anterior segment in the presence of POHS-like lesions. In contrast to that, our case did not show any inflammatory signs in the vitreous or in the anterior segment.

A review of the cases presented from Europe has revealed no previous reports showing the presence of linear streaks. An incidence of 5% has been reported in patients with symptomatic POHS in the USA.⁶

The streaks may result from loss of choriocapillaris and retinal pigment epithelium. So far there is no explanation for the linear aggregation of histoplasma spots, which is probably the mechanism of streak formation.

Other causes of streak-like lesions in the retina must be differentiated from those seen in POHS. These include migrating parasites, choroidal

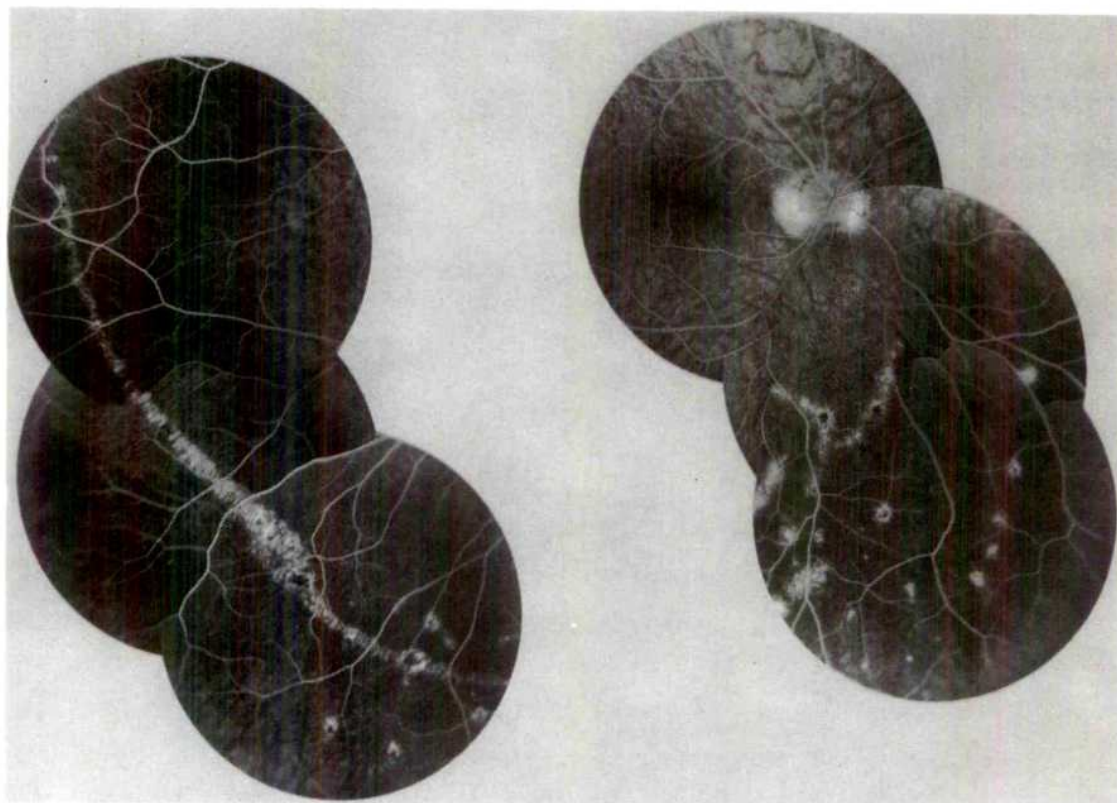


Fig 5 Case 5 fluorescein angiogram of the right eye.

ruptures, angioid streaks, lattice degeneration, demarcation lines, and streaks from ectatic areas, all of which can be distinguished by their characteristic appearances.

In conclusion, patients of European origin have fundus changes indistinguishable from POHS as seen in the USA; the abnormal signs include the circumferential linear scarring. The pathogenesis remains unproved. Schlaegel¹⁸ and we consider that the European syndrome may be caused by an agent similar to but different from *Histoplasma capsulatum*. Perhaps histoplasmosis is only one of several infections causing POHS.

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Trachoma and blindness in the Nile Delta: current patterns and projections for the future in the rural Egyptian population

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SUMMARY A population based survey of trachoma and blindness was conducted in a rural Nile Delta hamlet. Trachoma remains hyperendemic in this region. Active trachoma was common among preschool children; over half had moderate to severe disease. Of residents 25 years old 90% had substantial conjunctival scarring. Severe conjunctival scarring was commoner among women (84%) than men (58%), and three-quarters of older women had trichiasis/entropion compared with 57% of older men. Males and females had equivalent age specific rates of inflammatory disease. Blindness was associated with old age; 17% of residents aged 50 and over were blind. Estimates of blindness based on this survey and other surveys in Egypt indicate that blindness is still a serious public health problem in rural Egypt. The number of blind persons in Egypt will increase from an estimated 420 000 in 1980 to 868 000 by the year 2020. The current crude blindness rate of 1.8% is expected to increase to 2.3% in the year 2000 and to 3.2% in 2020.

As a part of an effort to develop a comprehensive approach to preventing blindness in Egypt we assessed the magnitude of trachoma and trachoma induced blindness in a rural community in the Nile Delta. The survey included environmental characteristics and behavioural observations.

Trachomatous inflammatory disease of the conjunctiva is characterised by the presence of follicles and papillary hypertrophy. Extension of blood vessels (pannus) over the cornea and conjunctival scarring are manifestations of chronic disease in susceptible individuals. Scarring of the conjunctiva produced by chronic inflammation during childhood causes the eyelids to deviate inward (trichiasis/entropion) long after the inflammatory disease has subsided. Constant abrasion of the eye by eyelashes causes corneal scarring and loss of vision in adult life.

Trachoma is considered to be the world's leading cause of preventable blindness. An estimated 500 million people have trachoma, with six million blind.¹

The condition has been endemic in Egypt since antiquity.

Material and methods

From January to March 1987 demographic, environmental, and clinical data were collected in the hamlet of Kafr* (population 1138) in the lower Nile Delta. Winter (December–March) is generally recognised to be the season with the lowest occurrence of eye infections (conjunctivitis) in Egypt.

Demographic data collected included age, sex, occupation, education, and religion. Socioenvironmental data collected included number of rooms (and sleeping rooms) in the household, construction material used, toilet facilities, animal and fedan (acreage) ownership, and television and radio ownership.

All residents were encouraged to undergo an ocular examination. In Kafr the response rate was 93%. In marked contrast, the response rate in Gamileya,* a second hamlet of equal population,

*Fictional names have been substituted for the two study sites.

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which was examined in the previous winter, was only 62%. Reasons for refusing eye examination in Kafr were almost always related to fear of examination. In Gamileya the lack of clear hamlet leadership also contributed to a reduced response rate. Similar results were observed in Gamileya, but owing to the substantial non-response rate in this hamlet data from Gamileya will not be presented in this paper.

CLINICAL EXAMINATION

Visual acuity was assessed at 6 m by a Landolt C eye chart. Clinical observations of trachoma were carried out with a Zeiss portable slit-lamp or loupes for children less than 1 year old. Scoring of the inflammatory and cicatricial signs of trachoma was carried out according to World Health Organisation recommendations.² These signs included trichiasis and/or entropion (inturned eyelids), lymphoid follicles and papillary hypertrophy on the upper tarsal

conjunctiva, conjunctival scarring, and corneal scarring. For each individual the intensity of inflammation (a measurement based on the degree of both lymphoid follicles and papillary hypertrophy) and degree of scarring were defined by the clinical disease in the worse eye.¹²

ANALYSIS

Data were analysed by the statistical package SPSS. Statistical representation of the cross-sectional data is presented in terms of disease prevalence and difference in prevalence (excess prevalence) by sex.

Results

POPULATION STRUCTURE

The age structure of the hamlet was pyramidal in shape: 25% of the population were under 6 years of age, 50% under 16 years, and only 10% over 50 years (Fig. 1). This age structure, which is characteristic of the current age structure of rural Egypt and of many

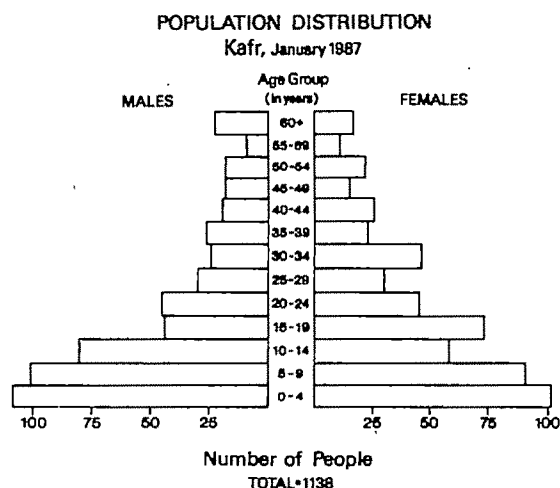


Fig. 1 Population distribution by age and sex.

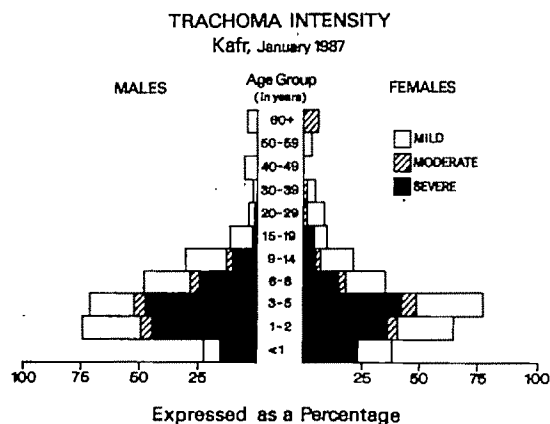


Fig. 2 Trachoma intensity by age and sex.

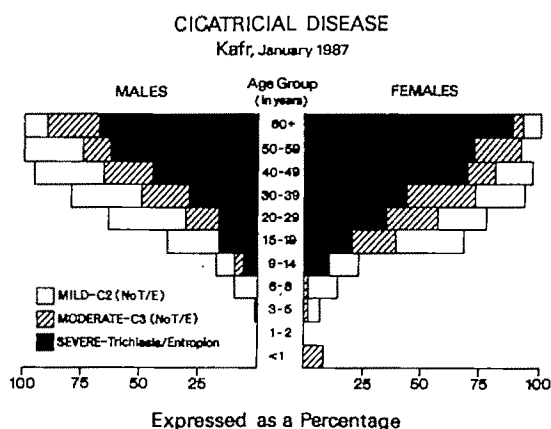


Fig. 3 Cicatricial disease by age and sex.

BLINDNESS & VISUAL IMPAIRMENT

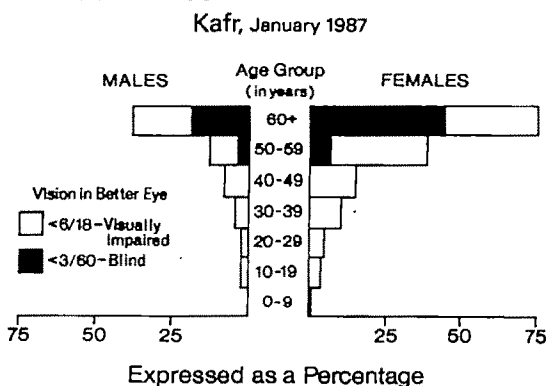


Fig. 4 Blindness and visual impairment by age and sex.

other developing countries, reflects the high birth rate. Size of households ranged from one to 35 family members with a mean of eight.

PREVALENCE OF INFLAMMATORY DISEASE

Active trachoma (severe and moderate intensity) was most common in the younger age groups (Fig. 2). Clinically active conjunctivitis was detected in infants as young as 2 months of age. One-third of the infants had inflammation of the upper tarsal conjunctiva before 2 years of age. The prevalence of active inflammation peaked at 59% among children 3 years of age and dropped off rapidly after age 5. Boys had a slightly higher prevalence of active trachoma than did girls. Among the adult population the prevalence of inflammatory disease was low.

PREVALENCE OF CICATRICAL DISEASE

Scarring of the conjunctiva was present in children as young as 2 years of age. The prevalence and severity of scarring increased with age, reflecting the cumulative nature of this sign (Fig. 3). By the age of 10 approximately one-half of the children had conjunctival scarring. Approximately 90% of all residents aged over 25 had moderate or severe scarring of the upper conjunctival plate. While no difference in overall scarring rates was detected between the sexes, 66 of 79 (84%) adult women had severe scarring compared with 46 of 79 (58%) adult men ($p < 0.005$). Inturned eyelashes (trichiasis/entropion), resulting from conjunctival scarring, was detected in 9- to 14-year-olds. Trichiasis and/or entropion was common among elderly residents; 59 of 79 (75%) of adult females had trichiasis and/or entropion compared with 45 of 79 (57%) adult men ($p < 0.02$).

BLINDNESS

Blindness was evaluated by the rigorous WHO criteria of $<3/60$ in the better eye.³ Blindness was associated with increased age; only one individual less than age 50 had vision in the better eye of less than $3/60$ (Fig. 4). Among men aged 50 and above 11% were blind. In terms of blindness in the community the oldest 10% of the population (aged 50 and over) accounted for 94% of all blindness. Corneal opacities accounted for 40% of the blindness; cataracts accounted for the remainder. Not unexpectedly, women were 2.5 times more likely to have corneal opacities than were men.

Discussion

Research by our group demonstrates that blinding trachoma is still hyperendemic in Egypt. Contrary to the belief in the late 1960s that the introduction of

chemotherapeutic agents and antibiotics would succeed in preventing many of these 'ophthalmias', active trachoma remains a common disease in rural Egypt.^{4,5}

Endemic trachoma was documented in Egypt as early as the 19th century BC.⁶ Cross-sectional studies in Egypt in the 1920s⁷ gave prevalence rates of 25% among infants under one year of age and 64% among children aged 1 to 2 years, findings that are similar to ours. Among older children and adults the rate of inflammatory or cicatrizing disease ranged between 84% and 99%. Attiah and El Togby reported an overall prevalence of infectious trachoma of 97%.⁸ Among a probability sample of 16 hamlets in a recent unpublished population based survey (1979-80) in Beheira governorate the level of inflammatory disease also was similar to that observed in the 1920s. More than one-quarter (28%) of the children aged 1 to 2 years had moderate to severe inflammatory trachoma. The rate of active trachoma dropped off rapidly after six years of age.

Investigations in the 1960s and 1970s demonstrated the endemicity of blinding trachoma in a number of neighbouring countries, including Morocco,⁹ Jordan,¹⁰ Tunisia,¹¹⁻¹³ and Sudan.¹⁴ Yet, with the notable exception of Tunisia, trachoma and blindness prevention still have not been identified as a priority by national health ministries in this region.

The World Health Organisation has determined that blindness constitutes a public health problem at the country level when nationwide blindness rates are 0.5% or greater.¹⁵ At the community level a community blindness rate of 1% or greater signifies that blindness is a public health problem. In Kafr the community rate of blindness was 1.5%. Furthermore in the 1960s a probability sample of households in Alexandria and in rural hamlets surrounding the city gave a crude blindness rate of 2.1%.^{16,17} Of the rural population 50 years and over 15% presented with visual acuity of $<3/60$ (20/400) in the better eye. As in our findings, women had a 13% excess prevalence ($p < 0.001$) when compared with men. The 1979-80 Beheira governorate survey (sample population of 8000) showed a crude rate of 1.9%, with 21% of the oldest age category (60+) having visual acuity of $<3/60$ in the better eye. Similarly, in the village of Kafr 30% of this age group was blind. Corneal opacities secondary to infection were the single leading cause of blindness in the Alexandria and surrounding hamlet survey. This was followed by cataract, the leading cause of blindness worldwide. In both the Beheira survey and in Kafr corneal opacities closely followed cataract as the second leading cause of blindness.

In the Egyptian setting blindness is often underestimated. A 1969 study comparing self selected and

Table 1 Blindness projections: rural Egyptian population

Year	Projected population at risk (rural) (A)	Projected population at risk 50+ years (B)	Percentage population 50+ years (C)	Blindness rate (D)	Projected rural blind 50+ years (E)	Proportion blind 50+ of total blind (F)	Projected total rural blind (G)	Crude blindness rate (J)
1980	20.98 m	2.10 m	11%	15%	314 700	93%	338 387	1.6%
2000	32.21 m	4.51 m	14%	15%	676 420	95%	712 021	2.2%
2020	44.66 m	8.93 m	20%	15%	1 339 800	96%	1 395 625	3.1%

Calculations:

1. (A) Rural population $\times$ (C) proportion of population 50+ years of age = (B) rural population 50+ years of age.
2. (D) Age specific blindness rate $\times$ (B) projected population 50+ years of age = (E) projected blind people 50+ years of age.
3. (E) Projected blind 50+ years of age / (F) proportion of total blind expected to be 50+ years of age = (G) projected total rural blind.
4. (G) Projected total rural blind / (J) projected total rural population = (J) crude blindness rate.

m=Million.

random sampling methods demonstrated underestimation of 130%, suggesting that self selected samples or projections based on self presentation may grossly underestimate blindness.¹⁸ This phenomenon was most prominent among adult women and individuals with postinfectious morbidity characterised by corneal opacities.

PROJECTIONS

While cross-sectional data have limited application to the assessment of risk factors for blindness in which the aetiology may be due to conditions in the distant past, they do allow projection of future levels of blindness. Current rates of inflammatory eye disease among the rural population of Egypt are unchanged from the 1920s. In addition, the age stratified prevalence of blindness in rural Egypt has remained relatively unchanged.

The population of Egypt is now estimated at 50 million. With the present annual growth rate of 2.8%, Egypt's population has been projected at 67 million in 2000 and 94 million in 2020.¹⁹ Life expectancy at birth is 57 years, and 10% of Egypt's population is 50 years of age or older. It is projected that this age group will account for 14% of the population in the year 2000 and 20% in the year 2020.

Childhood inflammatory trachoma has already produced conjunctival scarring—which will lead to adult onset trichiasis and blindness—in the current population over 15 years of age. It is not clear why inflammatory disease is more prevalent among young males and cicatricial disease is more prevalent among adult females. As this cohort ages, age specific rates of blindness can be expected to resemble current rates. In addition the age specific rate of blindness among adults 50 years of age and older can be expected to contribute to an increased crude prevalence of blindness. For the Egyptian rural population an age specific (50+ years) rate of blindness of 15%, as demonstrated in a 1969 survey of Alexandria and

surrounding rural areas,¹⁶ an unpublished survey of Beheira governorate, and our current work, will mean that up to 676 000 adults will be blind in the year 2000 and 1.3 million adults in the year 2020 (Table 1). Thus current crude blindness rates will increase from approximately 1.6% to 2.2% in the year 2000 and to 3.1% in the year 2020. In short, until prevention and treatment are more effective, blindness, at present a leading public health problem in rural Egypt, will increase substantially in frequency.

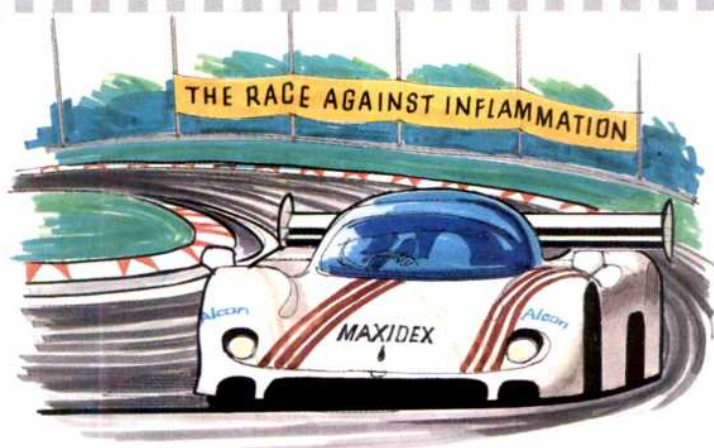
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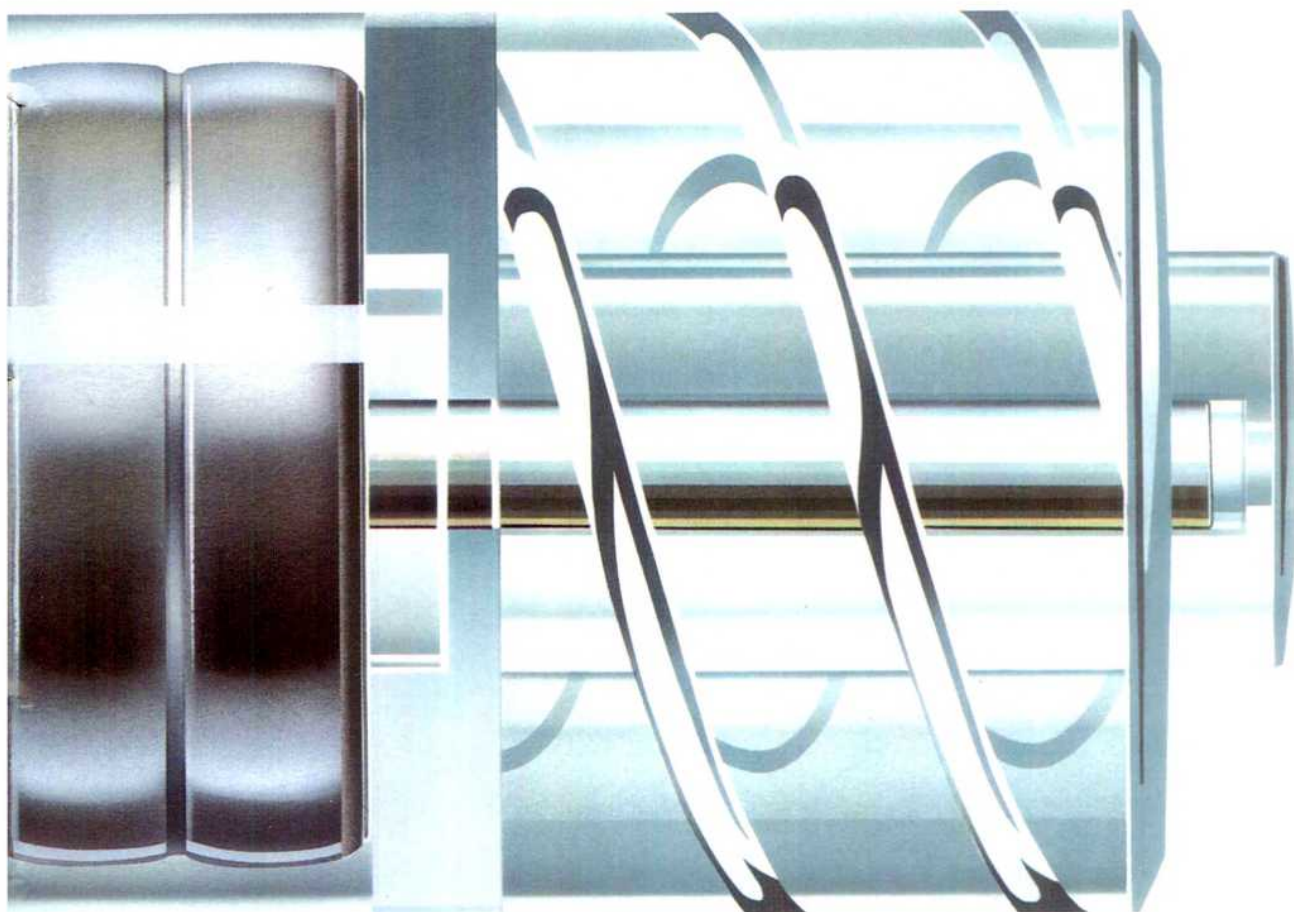
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Stability of one-stage adjustable suture for the correction of horizontal strabismus

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SUMMARY One-stage adjustable suture for strabismus correction, with the whole operation done under topical anaesthesia and adjustment done on the table, was performed on 45 consecutive patients. The stability of the post-adjustment result was studied by comparing the post-adjustment deviation on the operating table to that at six weeks and three months after operation. The stability was comparable to that following the usual two-stage adjustable suture. The original angle of deviation and the fusion status were found to have no bearing on the stability of the procedure.

The usual adjustable suture for the correction of strabismus, described by many authors,¹⁻¹⁰ is a two-stage procedure in which the recession with or without resection is performed as one operation and the adjustment is performed as a second procedure some hours later. A procedure involving multiple stages of adjustment has also been reported by Howard and Smith.¹¹

In this study the operation has been modified to a one-stage procedure. The operation is performed under topical anaesthesia and the adjustment done on the operating table. A similar procedure has been described by Thomson *et al.*¹² and Fells.¹³ The stability of the procedure is studied.

Material and methods

This operation has been performed since November 1986. It was offered to all adult patients and some selected children. They constituted a heterogeneous group of varied diagnoses and deviations. Forty-five consecutive patients followed up for three months after the operation were included in this study. There were 21 males and 24 females, ranging from 8 to 41 years old, average 21.8. There were 33 cases of exotropia and 12 of esotropia. The range of deviation was -20 prism dioptres (PD) to -80 PD with a mean of -46.8 PD for exotropia and +20 PD to +70 PD with a mean of +43.6 PD for esotropia. There were six patients with previous strabismus surgery, eight

with other eye operations (for example, cataract extraction), one patient with Duane's syndrome, and one with third nerve palsy. The details of each case will not be discussed in this report.

All the patients had a preoperative ocular examination and orthoptic assessment, including angle of deviation for near ($\frac{1}{2}$ m) and distant vision (6 m) with and without correction, measured by prism cover test; and fusional ranges measured by prism or major amblyoscope and stereopsis.

Premedication consisted of Neosporin (neomycin, gramicidin, and polymyxin B) eyedrops and Novesin (oxybuprocaine) 1 ml into the eye to be operated upon one hour before operation. All operations were performed by the same surgeon using the same procedure.

Two fixation sutures with 5-0 silk were inserted near the limbus at the points perpendicular to the muscles to be operated upon (that is, at 12 and 6 o'clock for the horizontal muscle operation). Recession was done first. The conjunctiva was opened over the insertion of the muscle to be recessed. A double-armed 6-0 Vicryl suture on a fine spatulated needle was placed in a whip-stitch manner in the muscle near its insertion and locked at the sides with a double-throw knot to prevent bunching up of the muscle. The muscle was then cut, and haemostasis was achieved with diathermy. The suture was then brought through the original insertion once only. The muscle was allowed to fall back to a point of proposed recession. The suture was then secured with a double-throw knot followed by a half-bow

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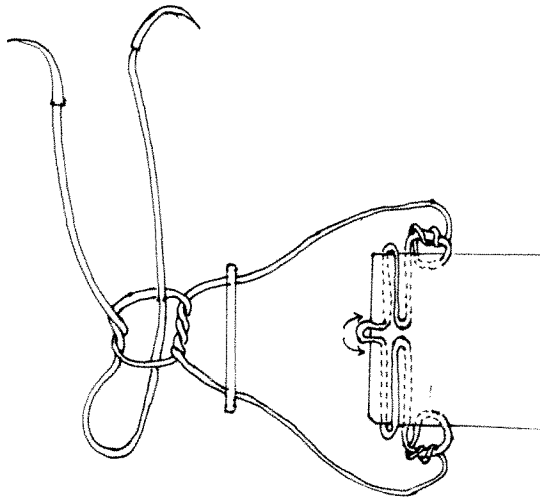


Fig. 1 Conjunctival incision over muscle insertion whip stitch in the muscle, double throw knot at sides of muscle, suture through original insertion once, and secured with a double throw followed by a half bow.

(Fig. 1). Any redundant suture was shortened.

Resection of the antagonist if indicated was done as in conventional strabismus surgery. Amethocaine 1% eyedrops was used to relieve pain whenever the patient complained on the operating table.

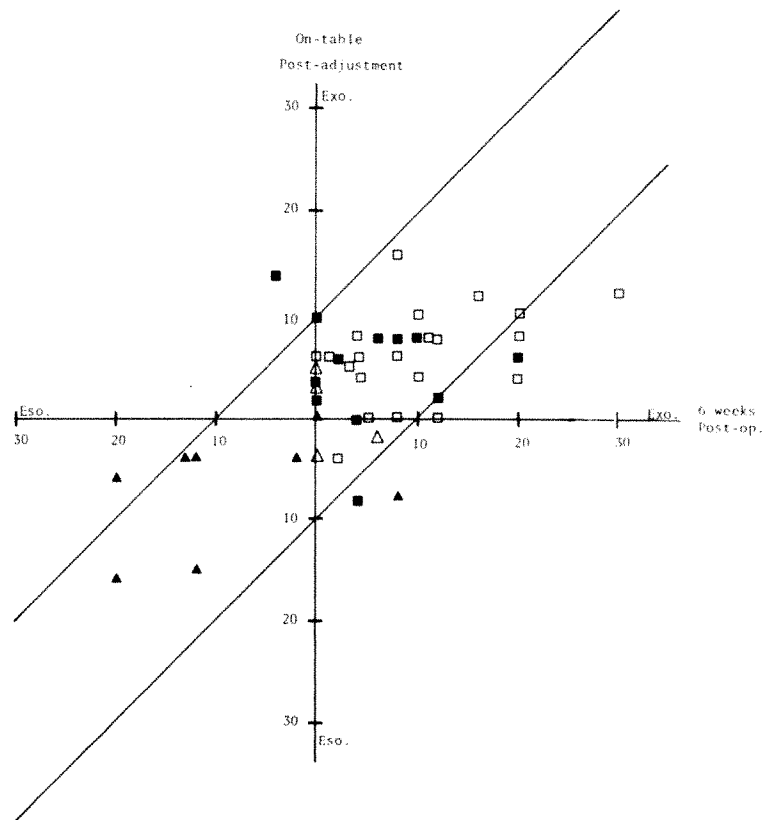
The patient was sat up on table after the drapes were removed. The deviation was measured for near and for distant vision by a prism cover test by an orthoptist. Any diplopia was also noted. Adjustment was made until there was no diplopia and the deviation was less than 10 PD in the primary position, with no abnormal head posture. In cases of large deviation which could not be corrected to within 10 PD an adjustment was made until there was 25% decrease in the range of movement.

The conjunctival incision was closed and the eye was padded for one more hour.

Results

The angle of deviation after adjustment on the operating table was compared with that six weeks and

Fig. 2 Stability of adjustable suture at six weeks for near vision. Measurements in prism dioptres. Closed square=preoperative exotropia with no fusion. Open square=preoperative exotropia with fusion. Closed triangle=preoperative esotropia with no fusion. Open triangle=preoperative esotropia with fusion.



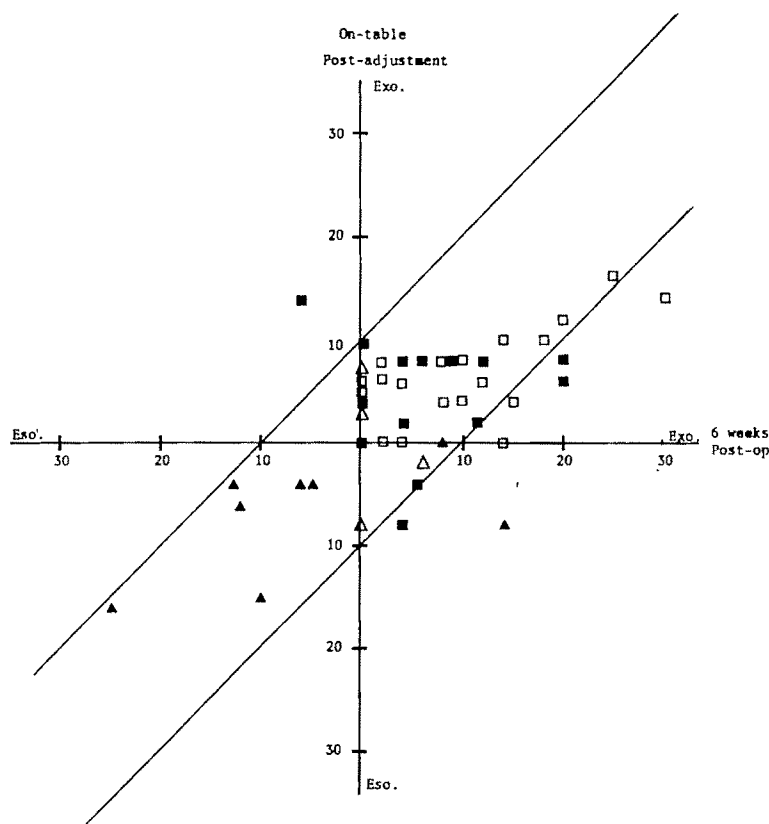


Fig. 3 Stability of adjustable suture at six weeks for distance. Measurements in prism dioptres. Symbols as in Fig. 2.

three months later and was plotted graphically (Figs. 2-5). The results are summarised in Tables 1 and 2. A change within 10 PD was considered satisfactory.

It was found that all cases of exotropia with an angle change greater than 10 PD drifted towards the original deviation. The drift in cases of esotropia varied.

Discussion

The success of strabismus surgery is apt to be unpredictable. The behaviour of the elastic tissue and muscles is the main reason for this problem. No formula can predict the final outcome. The adjustable suture has been developed to overcome this difficulty. The operation is generally performed as a two-stage procedure. In this study it is modified to a one-stage procedure. The stability of this one-stage adjustment is what has been examined here.

For esotropia (Table 1) the mean change of deviation at six weeks was 6.75 PD for near and 5.58 PD for distant vision, which is satisfactory. At three months the mean change of deviation increased to 10.17 PD for near and 7.67 PD for distant vision.

There was one esotropic patient with a post-adjustment deviation on the operating table of +4 PD that increased to +35 PD for near vision at three months after operation. Since there were only 12 esotropic patients in this study, an individual variation would cause a large change in the overall results: hence the high value for the mean change of deviation for near vision. The results for distant vision at three months are satisfactory.

For near vision 10 out of 12 (83%) esotropic patients and for distance 11 out of 12 (92%) esotropic patients had a change of less than 10 PD at six weeks. At three months they were eight out of 12 (67%) and nine out of 12 (75%) respectively.

For exotropia (Table 2) the mean change of deviation for near vision was 6.42 PD and for distant 6.79 PD at six weeks. At three months they were 7.27 PD and 7.52 PD respectively. At six weeks for both near and distant vision 26 out of 33 patients (79%) had a change of less than 10 PD. At three months for near vision it was 25 out of 33 (76%) and for distant 23 out of 33 (70%). This shows that the stability of the one-stage adjustable suture is satisfactory.

A comparison between this study and the report by

Fig. 4 Stability of adjustable suture at three months for near. Measurements in prism dioptres. Symbols as in Fig. 2.

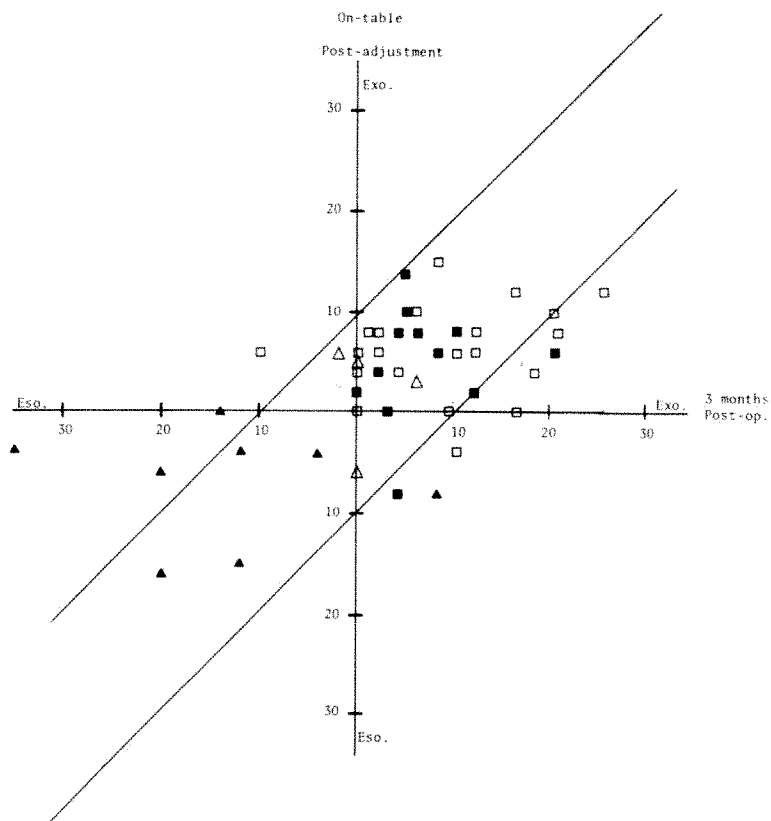


Fig. 5 Stability of adjustable suture at three months for distance. Measurements in prism dioptres. Symbols as in Fig. 2.

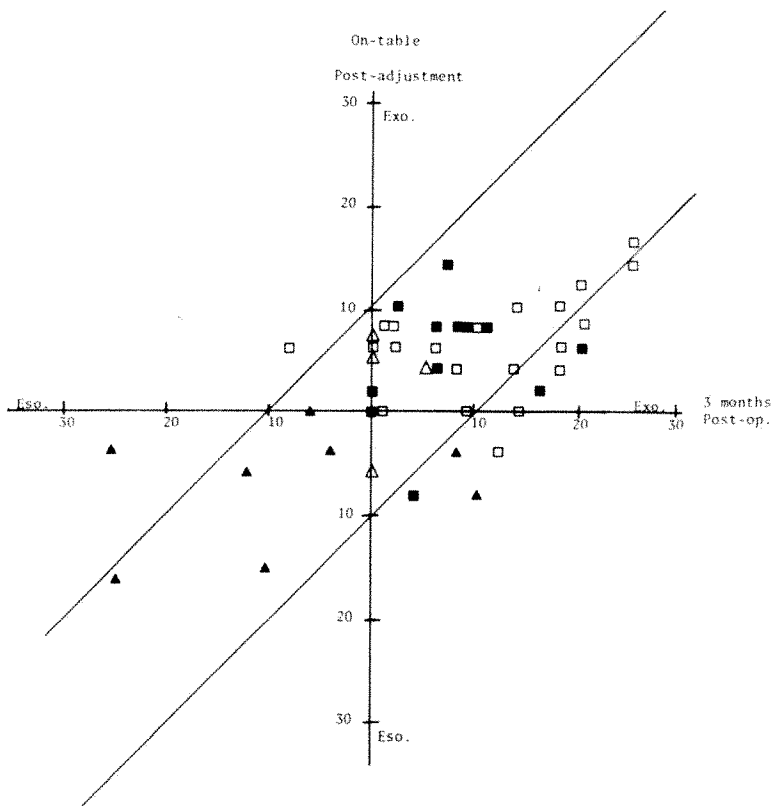


Table 1 Mean change of angle of deviation, the standard deviation, and the number of patients with an angle change of less than and greater than 10 PD for esotropia

	On table to 6 weeks		On table to 3 months	
	Near	Distant	Near	Distant
Mean change of deviation	6.75 PD	5.58 PD	10.17 PD	7.67 PD
SD	4.97	2.67	10.94	6.24
Patients with change <10 PD	10/12=83.3%	11/12=91.67%	8/12=66.7%	9/12=75%
Patients with change >10 PD	2/12=18.2%	1/12=0.83%	4/12=33.3%	3/12=25%

Table 2 Mean change of angle of deviation, the standard deviation, and the number of patients with an angle change of less than and greater than 10 PD for exotropia

	On table to 6 weeks		On table to 3 months	
	Near	Distant	Near	Distant
Mean change of deviation	6.42 PD	6.79 PD	7.27 PD	7.52 PD
SD	5.2	4.53	4.77	4.96
Patients with change <10 PD	26/33=78.8%	26/33=78.8%	25/33=75.8%	23/33=69.7%
Patients with change >10 PD	7/33=21.1%	7/33=21.1%	8/33=24.4%	10/33=30.3%

Hamming and Kunisch-Verslype¹⁴ on the two-stage procedure is shown in Table 3. There is no significant difference between the mean change of deviation for either near or distant vision at six weeks and three months. The ratio of patients with a change of more than 10 PD compares favourably with that of the two-stage procedure. Furthermore, Olivier¹⁵ reported that 23 out of 70 patients (33%) had a change of more than 10 PD at six weeks after the two-stage procedure. Thus the one-stage adjustable suture is at least as stable as the usual two-stage procedure.

The one-stage adjustable suture has further advantages over the usual two-stage procedure. It saves one or more surgical procedures. General anaesthesia and its attendant risks are avoided. Admission to hospital is not absolutely necessary, and most of the patients in this study were treated as outpatients.

The significance of fusion status and original angle of deviation is analysed in Table 4 for exotropia. Apparently they have no bearing on the stability. This is consistent with the result obtained by Hamming and Kunisch-Verslype.¹⁴ In esotropia; it is inconclusive owing to the small number of patients.

Table 3 Mean change of deviation and number of patients with an angle change greater than 10 PD are compared between this study and Hamming's¹⁴

	Hamming (6 weeks postop.)	Chow (6 weeks postop.)	Chow (3 months postop.)
Mean change of deviation (near)	8.82 PD	6.51 PD (SD=4.79)	8.04 PD (SD=6.62)
Mean change of deviation (distance)	5.88 PD	6.47 PD (SD=3.94)	7.55 PD (SD=4.62)
Patients with change >10 PD	9/34=26.47%	9/45=20%	12/45=26.67%
		Near:	Near:
		8/45=15.56%	13/45=28.8%
		Distant:	Distant:

Table 4 Fusion status and mean original angle of deviation between the patients with an angle change greater than and less than 10 PD are compared for exotropia

	Fusion		Mean original angle of deviation
	Positive	Nil	
Patients with Change <10 PD	14/23=61%	9/23=39%	45.4 PD
Patients with change >10 PD	6/10=60%	4/10=40%	50 PD

CONCLUSION

A one-stage adjustable suture for the correction of horizontal strabismus has been found to give satisfactory stability. It is suggested that it be considered for all adult patients and some selected children so long as their condition is stable and they are co-operative. Another requirement is an experienced strabismus surgeon. The operation is particularly suitable for small deviations where only a single muscle recession is necessary.

I would like to thank Dr T K C Liu, Dr P Ho, and Dr K F So for their helpful opinions and the staff of our orthoptic unit, with special thanks to Miss F Poon for collecting the data.

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Effect of spectacle use and accommodation on myopic progression: final results of a three-year randomised clinical trial among schoolchildren

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SUMMARY Two hundred and forty mildly myopic schoolchildren aged 9-11 years were randomly allocated to three treatment groups and the progression of myopia was followed-up for three years. The treatment groups were: (1) minus lenses with full correction for continuous use (the reference group), (2) minus lenses with full correction to be used for distant vision only, and (3) bifocal lenses with +1.75 D addition. Three-year refraction values were received from 237 children. The differences in the increases of the spherical equivalents were not statistically significant in the right eye, but in the left eye the change in the distant use group was significantly higher (-1.87 D) than in the continuous use group (-1.46 D) ($p=0.02$, Student's *t* test). There were no differences between the groups in regard to school achievement, accidents, or satisfaction with glasses. In all three groups the more the daily close work done by the children the faster was the rate of myopic progression (right eye: $r=0.253$, $p=0.0001$, left eye: $r=0.267$, $p=0.0001$). Myopic progression did not correlate positively with accommodation, but the shorter the average reading distance of the follow-up time the faster was the myopic progression (right eye: $r=0.222$, $p=0.0001$, left eye: $r=0.255$, $p=0.001$). It seems that myopic progression is connected with much use of the eyes in reading and close work and with short reading distance but that progression cannot be reduced by diminishing accommodation with bifocals or by reading without spectacles.

There are different opinions about the effect of spectacles on the progression of myopia. Those who believe that accommodation increases myopic progression usually recommend spectacles to be worn only for distant vision, and they often prescribe undercorrected lenses¹⁻³ or bifocals.^{4,5} Others think that spectacles should be worn continuously.^{6,7} Some authors suggest it makes no difference whether spectacles are devised for the special needs of children and worn either continuously or for distant vision only.^{8,9} These studies have been reviewed previously.^{10,11}

The purpose of this article is to report the final three-year results of a randomised trial comparing the effects of three different styles of correcting myopia among schoolchildren. The types of correction were fully corrected lenses for continuous use, for distant use only, and bifocals. In addition the

relation between myopic progression and accommodation, reading distance, and time spent on in reading and close work is examined.

Material and methods

Material and methods have been published in detail previously.^{10,11} Schoolchildren from the third and fifth grades of basic school who were referred to the outpatient clinic of the Central Hospital of Central Finland because of suspected myopia were considered for inclusion in the study. Their mean age was 10.9 years (range 8.8-12.8 yr), and they were recruited without selection while one of us (OP) was working in the outpatient clinic. The eye examination was carried out by the same ophthalmologist before inclusion in the study and at every control visit. To control possible observer bias the last examination was also carried out on 84 children by another ophthalmologist (AK) who did not know the group

Correspondence to O. Pärssinen, MD, Kannaksenk. 5, 40600 Jyväskylä, Finland.

assignments of the children. She assessed the refraction whenever she was available when the children came to the clinic. Refraction was measured about 45–60 minutes after administration of two drops of 1% cyclopentolate hydrochloride.

After exclusions the 240 children (spherical equivalents -0.35 to -3.0 D) were allocated to one of the three treatment groups by means of random sex-stratified codes in sealed envelopes. Before randomisation the children were asked whether they would like to participate in the study, and all agreed.

All the children received full correction for distant vision. The children allocated to the first group (termed continuous use group) were advised to use their glasses continuously. The children in the second group (termed distant use group) were advised to use them only when accurate distant vision was needed. The children in the third group (termed the bifocal group) received bifocals with 1.75 D near addition. The bifocals were the Coburn straight top 28, with a diameter of 65 mm. The top of the addition was fitted 2–3 mm below the centre of the pupil. All the children were advised to buy untinted lenses.

The child and the accompanying parent were given a questionnaire asking about background characteristics and habits.¹⁰ The questionnaire was given also during the control visits. At the time of inclusion in the study the three groups were similar in regard to most of the background characteristics, and the few small differences did not systematically favour any of the groups.

The children were invited three times by letter at one-year intervals to attend for follow-up examinations. The refraction values were adjusted for the varying follow-up times so that the last refraction was multiplied by 3×365 and divided by the exact number of follow-up days.

After allocation one of the boys in the continuous use group was excluded from comparison with the other treatment groups when we found that his sister has been included previously in a different group. Two children moved from the area, and their refraction values could not be obtained. The refraction of one further child was obtained from the files of his ophthalmologist.

The usual reading distance was measured by Clement Clark's accommodometer during every control visit. The average accommodation in reading was estimated from these readings and from the averages of the spherical equivalents of the right eye in two consecutive examinations. The following formulae were used to calculate accommodation between two control visits:

Continuous use: $ACC = (100/R_1 + 100/R_2) : 2 + (SFD_2 - SFD_1) : 2$

Distant use: $ACC = (100/R_1 + 100/R_2) : 2 + (SFD_2 + SFD_1) : 2$

Bifocals: $ACC = (100/R_1 + 100/R_2) : 2 + (SFD_2 - SFD_1) : 2 - 1.75$.

ACC=accommodation, R_1 and R_2 =reading distances in two consecutive visits, SFD_1 and SFD_2 =spherical equivalents of the right eye in two consecutive visits.

The average reading distance and accommodation for the whole follow-up was calculated from the consecutive values for annual reading distance and accommodation. The information concerning the amount of time spent on reading and other close work, on watching TV, and on outdoor activities was obtained from the questionnaire at the last examination.

The differences between the means of follow-up time, age, height, weight, reading distance, accommodation, refraction, and time spent on different activities for the three treatment groups were tested by Student's *t* test with the continuous age group as a reference group. The differences between the groups in compliance and in treatment problems were analysed by the χ^2 test. The associations between the refraction change and accommodation, reading distance and daily time spent on reading and close work, and outdoor activities and watching television were analysed by means of Pearson's product moment correlation coefficients.

Results

The follow-up times varied between 2.0 and 5.1 years, and in 95% of cases it was between 3.0 and 3.1 years. The means were similar in the different treatment groups (Table 1). There were no significant differences between the treatment groups in mean age at the end of the study. The bifocal group was 2 cm taller and 3.5 kg heavier than the continuous use group.

Compliance with the treatment was quite good (Table 2). Compliance was determined according to the children's reports of their use of spectacles during the previous year. In the continuous use and bifocal groups those children who had worn their spectacles continuously were classified as compliant. In all groups those wearing their spectacles at various times were classified as partly compliant. In the distant use group those wearing spectacles for distant vision

Table 1 Background characteristics of treatment groups at the end of the study (means and SD)

	Distant use	Continuous use	Bifocals
Number of boys	38	40	40
Number of girls	41	39	39
Mean follow-up (yr)	3.0 (0.1)	3.0 (0.1)	3.0 (0.3)
Mean age (yr)	13.9 (1.0)	14.0 (1.1)	14.0 (1.0)
Mean height (cm)	161 (10)	162 (8.3)	164 (8.1)
Mean weight (kg)	49.2 (10.1)	49.0 (8.7)*	52.5 (9.6)

* $p < 0.05$, *t* test, continuous use group as the reference group.

Table 2 Compliance and problems with the treatment

	Distant use	Continuous use	Bifocals
Compliant (%)	89	79	76
Partly compliant (%)	6	18	21
Non-compliant (%)	5	3	3
Good satisfaction (%)	91	86	78
Glasses broken or lost at least once during the last year (%)	19	25	14
at least once during the follow-up (%)	37	42	28
Accidents during the last year (%)	10	12	12

only, or only occasionally, were classified as compliant, and those wearing them constantly were classified as non-compliant. The proportions of compliant children somewhat increased in the continuous use and distant use groups during the follow-up.

During the first year the bifocal lenses were changed to monofocals for four children. No such changes were needed after the first year. One of the four whose lenses were changed moved to another locality during the first year and the results of only her first year refraction were received. In the case of one child the use of bifocals was discontinued because of increasing exophoria, and two children regarded the bifocals as inconvenient and ugly and discontinued their use.

Children were relatively satisfied with their spectacles according to the answers given in the questionnaire (Table 2). In each treatment group there were two to four children who were otherwise satisfied but did not see clearly enough, and they were also classified as satisfied. In the bifocal group six children considered the glasses ugly or the line between the segments disturbing. Otherwise the

reasons for dissatisfaction were similar in the three groups. For example, glasses were regarded as impractical, and they were a nuisance in sports and other activities. The degree of satisfaction did not significantly change during the follow-up. The glasses were broken or lost somewhat more often in the continuous use group than in the other two groups.

There were no significant differences between the groups in accidents during the last three months or during the last year. School averages were also similar and varied between 7.9 and 8.0 (in Finland grades are given from 4 to 10).

There were no differences in reading distance between the groups, but the calculated mean accommodation for the whole follow-up in reading was significantly less in the distant use and bifocal groups than in the continuous use group (Table 3). The time spent daily on reading and near work was similar in all the treatment groups. Children in the bifocal group reported spending less time daily on sports and outdoor activities than those in the continuous use group. The watching of television was less in the distant use group than in the continuous use group.

The increase in myopia measured both in terms of change since the beginning of the study and group means was greatest in the distant use group in the left eye (Table 4). In the right eye the differences between the groups were not statistically significant. The increase in astigmatism was also somewhat smaller in the continuous use group than in the others, but the differences were not statistically significant.

The increase in myopia was faster among girls than among boys. The same was seen in all the treatment groups, though there were no refraction differences between boys and girls at the beginning of the study. The time spent daily on reading and near work was nearly the same for both boys and girls (boys 3.2 h, and girls 3.3 h). Boys spent more time on sports and outdoor activities than girls (boys 3.0 h and girls 2.5 h).

The reliability of refraction readings is given in Table 5. The ophthalmologist AK, who did not know the group assignment of the subjects, found spherical equivalents which were -0.11 D to -0.27 D more myopic than the respective values of ophthalmologist OP. The differences did not favour any of the treatment groups and least of all the continuous use group. The differences were not statistically significant. A possible explanation of the differences is the time between the two examinations. The children usually had to wait 15–30 minutes after refraction in the case of OP, so that the effect of the cycloplegic had diminished, so that the refractions done by AK were perhaps more myopic.

The shorter the average reading distance of the

Table 3 Reading distance, accommodation, and time spent in different activities among treatment groups during the last year (mean and SD)

	Distant use	Continuous use	Bifocals
n	79	79	79
Reading distance (cm)	27 (5)	27 (5)	28 (5)
Accommodation in near work (D)	1.0 (1.0) **	3.5 (1.0) **	1.7 (0.8)
Daily time used for reading and other near work (h)	3.1 (1.0)	3.4 (1.0)	3.2 (0.9)
Daily time used for outdoor activities (h)	2.8 (1.4)	3.0 (1.2) **	2.4 (1.1)
Daily time spent watching TV (h)	2.1 (0.9) **	2.5 (0.9)	2.4 (1.0)

** $p < 0.01$, t test, continuous use group as the reference group.

Table 4 Refraction in different treatment groups, means in dioptres (and SD)

	Distant use	Continuous use	Bifocal use
Change of spherical equipment since entry			
Boys and girls right eye	-1.76 (1.0)	-1.48 (0.9)	-1.67 (0.9)
left eye	-1.88 (1.0) **	-1.46 (0.9)	-1.58 (0.9)
Boys right eye	-1.60 (1.0)	-1.36 (0.9)	-1.39 (0.7)
left eye	-1.73 (0.9) *	-1.37 (0.8)	-1.29 (0.7)
Girls right eye	-1.92 (1.0)	-1.59 (1.0)	-1.96 (1.0)
left eye	-2.02 (1.0) *	-1.54 (1.0)	-1.89 (1.0)
Change of astigmatism			
Boys and girls right eye	-0.23 (0.4)	-0.14 (0.4)	-0.23 (0.4)
left eye	-0.23 (0.3)	-0.15 (0.3)	-0.22 (0.4)
Spherical equivalent at the end of the study			
Boys and girls right eye	-3.11 (1.2)	-2.92 (1.1)	-3.17 (1.1)
left eye	-3.32 (1.1) *	-2.94 (1.1)	-3.10 (1.2)
Boys right eye	-2.95 (1.2)	-2.83 (1.2)	-2.86 (1.0)
left eye	-3.20 (1.1)	-2.92 (1.1)	-2.76 (1.1)
Girls right eye	-3.27 (1.2)	-3.01 (1.0)	-3.48 (1.3)
left eye	-3.43 (1.1)	-2.97 (1.0)	-3.45 (1.2)

* $p < 0.05$, ** $p < 0.01$, t test. continuous use group as the reference group.

follow-up time the faster was the rate of myopic progression of the right eye (Table 6), though the bifocal group were an exception. About the same correlations were true also with reading distance of the last year and with the left eye. The correlation between accommodation and myopic progression was significant only in the distant use group; the less the accommodation the faster was myopic progression. This correlation, however, depends on the calculation formula; the higher the myopia and myopic progression the more was the accommodation value reduced when reading was done without spectacles.

The more the time spent on reading and close work the faster was the rate of myopic progression. The correlation between myopic progression and outdoor

Table 5 Spherical equivalents of 84 children in the last control visit studied by two ophthalmologists, means in dioptres (and SD) are shown. Number of children: 25 in the distant use group, 27 in the continuous use group, and 32 in the bifocal group

	Ophthalmologist OP	Ophthalmologist AK	Difference
Right eye			
distant use	-2.83 (0.9)	-3.07 (1.1)	-0.24
continuous use	-3.22 (1.0)	-3.33 (0.9)	-0.11
bifocal	-3.26 (1.4)	-3.42 (1.3)	-0.16
Left eye			
distant use	-3.00 (0.9)	-3.21 (1.0)	-0.21
continuous use	-3.14 (0.9)	-3.32 (0.9)	-0.18
bifocal	-3.15 (1.4)	-3.38 (1.2)	-0.23

Table 6 The Pearson's product moment correlation coefficients (r) and p values (p) between myopic progression in the right eye and the average reading distance and accommodation during the whole follow-up, and the time spent daily on different activities during the last year

		<i>Distant use (n=64-79)</i>	<i>Continuous Bifocal use (n=64-79)</i>	<i>(n=60-79)</i>	<i>All (n=188-236)</i>
Reading distance	r	-0.290	-0.278	-0.105	-0.222
	p	0.006	0.009	0.187	<0.001
Accommodation	r	0.260	-0.073	0.046	0.114
	p	0.019	0.284	0.363	0.059
Daily time on reading and near work	r	-0.313	-0.287	-0.241	-0.253
	p	0.003	0.005	0.016	<0.001
Daily time on outdoor activities	r	0.286	0.139	0.013	0.174
	p	0.006	0.111	0.455	0.004
Daily time on watching TV	r	-0.079	0.202	0.050	0.075
	p	0.246	0.037	0.333	0.126

activities was the opposite, but it held true only in the distant use group. The more time spent daily on watching TV, the less was the myopic progression in the continuous use group.

Discussion

The results of this three-year follow-up show that neither the use of bifocals nor avoiding the use of spectacles in reading slows down myopic progression. On the contrary myopic progression was somewhat slower among those who were advised to use spectacles all the time. In some animal experiments blurring of vision has induced myopic progression.¹² It has also been suggested that astigmatism when uncorrected could induce myopic progression.¹³ Uncorrected myopia in cases where the use of spectacles is avoided so as to be used only for distant vision might have the same kind of effect.

In previous studies the prevalence of myopia has been shown to be connected with reading and close work.¹⁴⁻¹⁶ In this study the progression of myopia among myopic children was also related to much reading and close work. So it seems that not only the prevalence of myopia but also the degree of myopia is connected with the amount of reading.

During reading without spectacles the relation between accommodation and convergence is changed. There is also obviously more need of convergence and less need of accommodation. In this study there was a positive correlation between short reading distance and rapid myopic progression, but the correlation was negative or nil between myopic progression and accommodation. This result runs counter to the view that accommodation in reading is an important factor in myopic progression.¹⁷ These

results may lend support to the theory that convergence is one reason for myopic progression,¹⁸ but the question still remains whether the short reading distance is a reason for the faster myopic progression or the consequence of higher myopia. The differences in myopic progression between the treatment groups cannot be explained by differences in the reading distances, as they were statistically the same in all the groups.

Children in the bifocal group spent somewhat less time on sports and outdoor activities than did the others. The lower segment of bifocals may disturb vision and is perhaps the reason for that finding. Why the distant use group watched TV less than the others is not clear. Previously it has been found that myopia begins earlier among girls than boys,¹⁹ and in some studies there was a higher prevalence of myopia among women than men.²⁰ In this study the progression of myopia was faster among girls than boys in all the treatment groups, though their refractions were similar at the beginning of the study. It is difficult to say whether that difference depends on the small differences in time spent on reading and close work and on sports and outdoor activities.

On the basis of these results the continuous use of fully corrected spectacles can be recommended for myopic children. It cannot yet be stated whether the same holds true for myopic adults. To determine this we are planning a similar study with a group of late-onset myopic adults.

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Subepithelial corneal deposits in IgG λ myeloma

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SUMMARY A 46-year-old female presented with disseminated IgG λ myeloma and unusual, translucent, subepithelial deposits in the periphery of both corneas. Electrophoretic studies showed that the deposits consisted of an IgG λ paraprotein identical to that found in the serum. Minute amounts of the paraprotein were also present in the tears.

Corneal crystals are well documented in patients with hypergammaglobulinaemia.¹⁻⁷ The crystals may be found at various depths in the cornea and are composed of immunoglobulin similar to that found in the serum.^{1,4,6,7} In two patients non-crystalline stromal deposits of immunoglobulin have been reported^{8,9}; in one case⁹ the deposits extended into the epithelium. We report on a patient with large subepithelial deposits of immunoglobulin in the periphery of both corneas—a presentation that has not been previously described.

Correspondence to Dr John C Hill, Department of Ophthalmology, Medical School, University of Cape Town, Cape Town, South Africa.

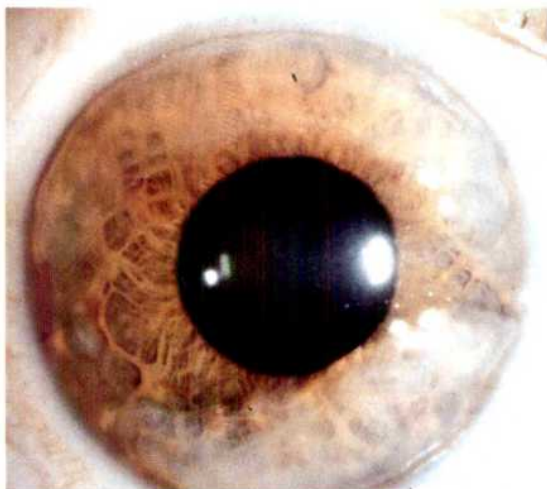


Fig. 1 Clinical photograph of the right cornea showing translucent peripheral deposits.

Case report

A 46-year-old female presented in October 1985 with a history of bilateral mild ocular irritation and photophobia. Corrected visual acuities were 6/6 in both eyes. Translucent subepithelial deposits were present in the periphery of both corneas, with a lucid zone of normal cornea separating them from the limbus. The deposits were larger in the upper and



Fig. 2 Slit-lamp photograph of the right cornea showing subepithelial location of the deposits with extension into the stroma. Note region of normal cornea between lesion and limbus.

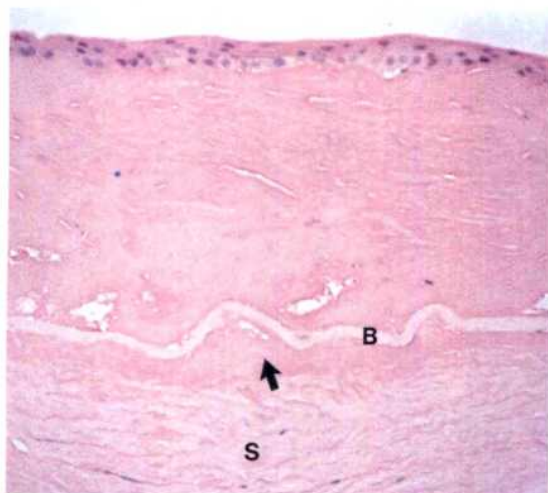


Fig. 3 Medium power haematoxylin and eosin stained section. Amorphous eosinophilic material separates epithelium and Bowman's layer (B) and extends (arrow) into anterior stroma (S).

lower regions of the cornea (Figs. 1 and 2). The remainder of the ocular findings were normal apart from a small pterygium on the left eye.

Physical examination showed an obese woman with mild angina and hypertension. She had been followed up since February 1984 with a high erythrocyte sedimentation rate of 120 mm/h and an unexplained IgG λ monoclonal gammopathy of approximately 40 g/l with associated immunoparesis. Repeated skeletal surveys and bone marrow examinations had shown no evidence of myeloma.

Bence Jones protein was subsequently found in the urine, and renal biopsy confirmed a λ chain nephropathy. Electromyographic studies showed extensive denervation in the intrinsic muscles of both hands and feet with normal proximal muscles, in keeping with a myeloma induced polyneuropathy. A diagnosis of disseminated myeloma was made, and treatment with upper and lower half body irradiation was given in early 1987.

The patient remains well but her paraprotein levels are high and the corneal deposits are unchanged. She has, however, developed granular deposits beneath the anterior and posterior lens capsules in a sunflower distribution. Her visual acuities have dropped to 6/9.

Material and methods

A corneal lamellar biopsy was taken and the specimen fixed in 10% buffered formalin. Routine histological stains including those for amyloid were employed as well as a battery of immunoperoxidase stains for immunoglobulins. A further small piece of

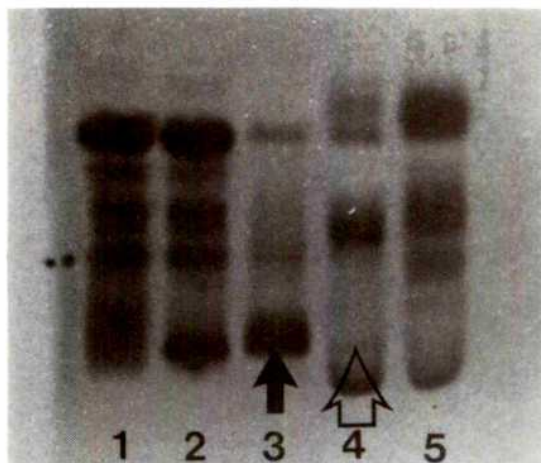


Fig. 4 Agarose gel electrophoresis. Lane 1=control serum; lane 2=patient's serum; lane 3=solubilised corneal lesion; lane 4=patient's tears; lane 5=control tears. A cathodally migrating paraprotein is present in the patient's serum and corneal lesion (closed arrow) with a faint band in the patient's tears (open arrow).

tissue was fixed in glutaraldehyde and submitted for electron microscopy.

A corneal scrape of the lesion in one eye was performed. The epithelium and deposit were removed as a plaque, which separated easily from Bowman's layer. The scrapings were solubilised in 0.9% NaCl and electrophoresed on agarose gel by the Paragon system and on polyacrylamide gel.¹⁰ Immunofixation electrophoresis was performed on agarose gel by the method of Johnson¹¹ with minor modification.

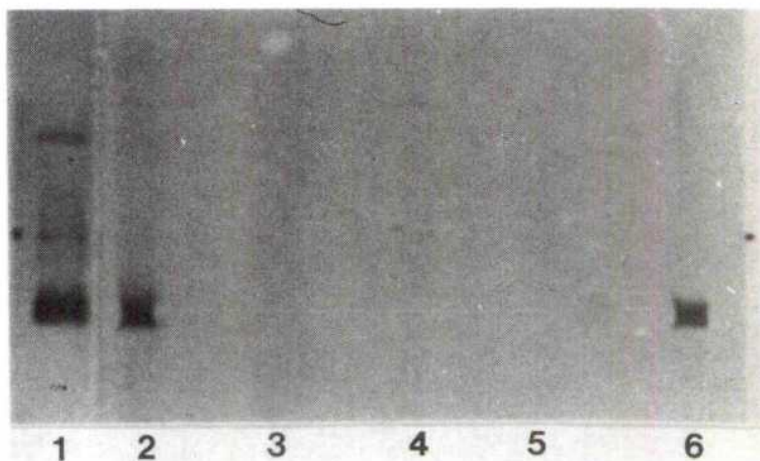
Tears were collected from the medial canthal region with capillary tubes.

Results

Light microscopy showed large amounts of amorphous eosinophilic material between Bowman's layer and the epithelium, with some extension into the superficial stroma (Fig. 3). The amorphous material did not stain for amyloid. Immunoperoxidase stains showed some staining for IgG and IgA, but staining for α and λ light chains did not differentiate between the two. Electron microscopy showed no evidence of the distinct fibrillar ultrastructure typical of amyloid.

Agarose gel electrophoresis (Fig. 4) showed the patient's serum to contain a cathodally migrating paraprotein. The solubilised corneal lesion contained a similarly migrating protein. Immunofixation electrophoresis (Fig. 5) showed the protein to be an IgG λ paraprotein identical to that found in the serum.

Fig. 5 Immunofixation electrophoresis of solubilised corneal deposits. Lane 1=standard electrophoresis; lane 2=anti- γ ; lane 3=anti- γ ; lane 4=anti- μ ; lane 5=anti- κ ; lane 6=anti- λ . Staining in lanes 2 and 6 identify the paraprotein as IgG λ .



On sodium dodecyl sulphate (SDS)-polyacrylamide gel electrophoresis the paraproteins in the serum and the cornea were shown to be of a similar molecular weight, namely, +150 000 Daltons (data not shown). Electrophoresis of the tears showed only a trace of the paraprotein.

Discussion

The patient was hypergammaglobulinaemic for over 20 months before her ophthalmic examination. Her ocular symptoms were mild, without the severe photophobia⁹ or loss of visual acuity^{1,8} reported by other workers.

Corneal crystals are a well documented finding in hypergammaglobulinaemia.¹⁻⁷ Only two patients have been reported as having non-crystalline deposits.^{8,9} In both the deposits were located in the stroma. By means of immunohistological techniques the crystals and deposits have been shown to consist of immunoglobulins. In our patient the deposits were predominantly subepithelial, and the large amounts of tissue obtained by scraping enabled us to perform electrophoretic studies. The corneal deposits consisted almost entirely of IgG λ paraprotein identical to that found in the serum.

We thank Dr R Bowen for the histological preparations. The study was partially funded by the South African Medical Research Council.

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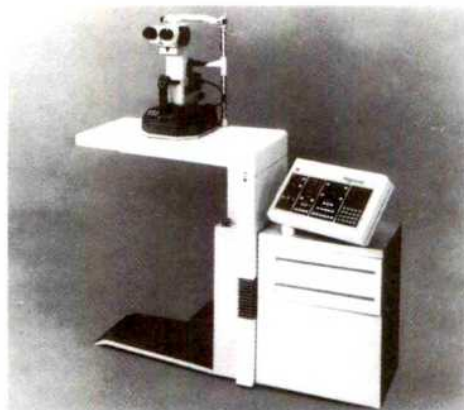
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Magnetic resonance imaging of intraocular foreign bodies

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SUMMARY Magnetic resonance imaging was performed with a low field strength scanner (0.08 tesla) on 15 bovine eyes into which had been inserted various magnetic and non-magnetic foreign bodies. The precise location of the foreign bodies was determined by dissection. Magnetic resonance imaging was accurate in locating 11 of the 13 non-magnetic foreign bodies in this study. In addition a further five bovine eyes containing 10- to 20-mm long steel needles were scanned and dissected. No ocular damage attributable to movement of the foreign bodies could be seen.

The identification and localisation of intraocular foreign bodies relies primarily on soft tissue x-ray. Computerised tomography scanning has been shown to be useful but has some limitations.¹ It may be inadequate for some radiolucent foreign bodies or those adjacent to the sclera. Ultrasound is also useful, especially if the foreign body is large or for visualising the complications of penetrating injuries such as retinal detachment or vitreous haemorrhage. However, ultrasonic transducers are frequently not suitable for study of the acutely injured eye, because they require either direct contact with the eye or indirect coupling via a waterbath system.

The purpose of this study was to determine whether foreign bodies could be usefully detected in ocular tissue by magnetic resonance imaging. Vitreous haemorrhage and intravitreal air were imaged for comparison. In addition the eyes were inspected by dissection to determine any damage resulting from movement of the foreign bodies during the scanning technique.

Material and methods

FOREIGN BODIES

A variety of organic and metallic foreign bodies were used in this study (Table 1). One copper, two steel, two aluminium, and two lead intraocular metallic foreign bodies were imaged and varied in size from 2×1×1 mm to 5×3×2 mm. Two fragments of soft

wood, two of laminated siliconised glass (windscreen glass), one fragment of graphite (pencil lead), one polyethylene, and two gravel fragments were scanned. The smallest was 3×2×2 mm and the largest 5×3×3 mm.

In addition five eyes which each had a single 10- or 20-mm long steel needle inserted were scanned and dissected.

METHOD OF INSERTION

The foreign bodies were inserted into fresh bovine

Table 1 *Intraocular foreign bodies inserted into bovine eyes*

	Position	Size	Detection: yes (Y) or no (N)
Aluminium	post. choroid	5×3×2	Y
	ant. vitreous	4×3×0.1	Y
Copper	ant. vitreous	3×2×0.25	Y
Lead	post. choroid	2×1×1	N
	ant. vitreous	2×1×1	Y
Glass	post. choroid	3×2×2	N
	ant. vitreous	3×2×4	Y
Graphite	post. choroid	3×2×2	Y
Polythene	post. vitreous	3×2×1	Y
Steel	post. choroid	3×3×0.2	Artefact
	post. choroid	3×4×0.2	Artefact
Gravel	post. choroid	3×2×3	Y
	ant. vitreous	5×3×3	Y
Soft wood	post. choroid	4×2×2	Y
	ant. vitreous	4×2×2	Y
Controls	Intravitreal air		
	Intravitreal haemorrhage		
	Wound only		
	Wound and suprachoroidal Haemolysis		

eyes through a triangular scleral flap at the posterior pole with microforceps to place the foreign bodies in the suprachoroidal space or the vitreous gel. To avoid the introduction of air the foreign bodies were inserted into the suprachoroidal space under sodium hyaluronate (Healonid).

Two control eyes were similarly operated upon but without the insertion of foreign bodies to determine whether any scanning artefact was induced by the wound or the presence of Healonid. 0.5 ml of human blood was injected into the vitreous by a 23 gauge needle through the pars plana into the vitreous

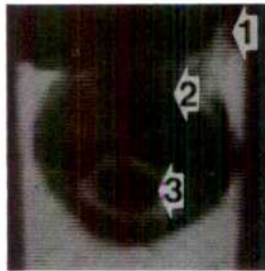


Fig. 1



Fig. 2

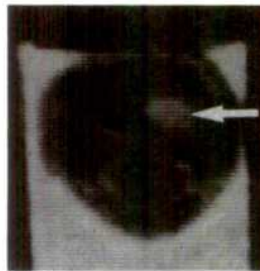


Fig. 3



Fig. 4

Fig. 1 A proton density image of a bovine eye with 1.0 ml of intravitreal air. Arrow 1 shows the optic nerve, arrow 2 the intravitreal air, arrow 3 the lens. Fig. 2 An inversion recovery image of 1.0 ml of intravitreal air (arrow). Fig. 3 A proton density image of 0.5 ml of intravitreal haemorrhage (arrow). Fig. 4 An inversion recovery image of 0.5 ml of intravitreal haemorrhage (arrow).

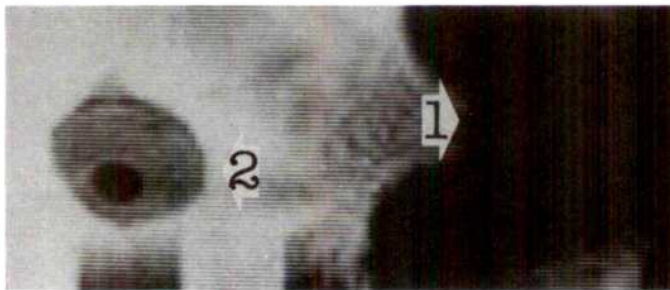


Fig. 5 The T1 weighted image of the artefact from a ferromagnetic foreign body. Arrow 1 shows the position of the globe with a 3x3x0.2 mm steel foreign body, but the image of the globe is obscured by the effect of the presence of only a small steel foreign body. Arrow 2 shows a globe with a 4x2x2 mm soft wood fragment for comparison.



Fig. 6



Fig. 7



Fig. 8

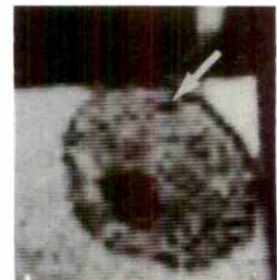


Fig. 9

Fig. 6 A T1 weighted image of an aluminium fragment (4x3x0.1 mm) in the anterior vitreous (arrow). Fig. 7 A T1 weighted image of a gravel fragment (3x2x2 mm) in the posterior suprachoroidal spaces (arrow). Fig. 8 A T1 weighted image of a soft wood fragment (4x2x2 mm) in the posterior suprachoroidal space (arrow). Fig. 9 A T1 weighted image of a high density polyethylene foreign body (3x2x1 mm) in the posterior vitreous (arrow).

gel. Similarly 1.0 ml of air was injected into the vitreous gel of another eye.

MAGNETIC RESONANCE SCANNING TECHNIQUE

The eyes were immersed in a bath of copper sulphate in a Perspex container which provided a background intensity against which the globe could be visualised. The globe was imaged transaxially with a four-coil air cored resistive magnet of 0.08 T main field strength. The imager has a resonant frequency for hydrogen of 3.4 MHz. An interleaved pulse sequence consisting of 90° radiofrequency pulses every 1000 ms with alternate pulses preceded by 180° inversion was used. From the sequence information it is possible to display a saturation recovery image (proton density), inversion recovery image, T1 calculated image, T1 weighted image (image formed by the subtraction of two interleaved signals which gives anatomically detailed images with T1 weighting.²³ 8 mm slice thicknesses were taken with a surface coil.

METHOD OF LOCALISATION

After being imaged the eyes were dissected by removal of the anterior globe by incision through the pars plana. The location of the foreign body was noted in relation to the optic nerve and the wound site and compared with the magnetic resonance images. Any change in the position of the foreign body or damage to the intraocular structures was noted.

Results

Control eyes showed no significant artefact from the wound site or the injection of Haelonid. 1.0 ml of injected air appeared on scan as an area of low signal on proton density (Fig. 1) and inversion recovery (Fig. 2). Fresh vitreous haemorrhage was seen as an area of high proton density (Fig. 3) and low inversion recovery (Fig. 4). Steel foreign bodies caused a large artefact which obscured all detail of the globe despite the small size of the foreign bodies used (Fig. 5).

The other foreign bodies as small as 2×1×1 mm were easily visualised as low intensity defects on inversion recovery, proton density, and T1 weighted images (Figs. 6, 7, 8, 9). They were seen most clearly on the T1 weighted images.

In two cases the foreign bodies were not detected, when a piece of glass and a lead foreign body were placed in the suprachoroidal space. Graphite gave a small artefact which did not obscure detail of the globe significantly.

It was not possible to distinguish the different materials by this scanning technique.

No change in the position of the foreign bodies or damage to the intraocular structures was found, including those with large ferromagnetic foreign

bodies (needles). The retinæ were damaged only at the site of insertion of the foreign bodies.

Discussion

The present study has shown that magnetic resonance imaging is capable of detecting small non-ferromagnetic foreign bodies in ocular tissue. Even at the low field strength used the foreign bodies were plainly visible in 11 of the 13 eyes and localisation was possible. They are readily differentiated from other ocular tissues. However, as with computed tomography scanning, foreign bodies close to the sclera are more difficult to detect. In this series two of the six suprachoroidal foreign bodies were not detected, whereas similarly sized foreign bodies in the vitreous gel were detectable. Sclera gives low proton density and inversion recovery signals similar to the foreign body characteristics and may therefore obscure foreign body detail.

Vitreous haemorrhage resulting from a penetrating injury from an intraocular foreign body is unlikely to reduce foreign body detection. In this study the characteristics of haemorrhage on magnetic resonance imaging were shown to differ from those of foreign body material (a low T1 and high proton density signal). In addition the T1 signal will increase as the vitreous haemorrhage ages.⁴⁵ Intraocular air may be confused but is unlikely to be present unless vitreoretinal surgery has been performed.

Magnetic resonance scanning using more modern scanners of higher field strength is likely to give higher resolution images and allow thinner slices,⁶⁷ which would improve detection and localisation. However, there is a distinct risk of torsional forces being applied to the ferromagnetic foreign body, thereby causing intraocular complications.⁸ Indeed ferromagnetic foreign bodies have been shown to move in gelatin and cause retinal tear, dialysis, and detachment in rabbits after magnetic resonance imaging with high field strength systems.⁹ One case of vitreous haemorrhage has been described following scanning with a 0.35 T imager of a ferromagnetic foreign body.¹⁰ Reports of magnetic resonance imaging of foreign bodies elsewhere in the human body—for example, intracranial aneurysm clips—have not included significant complications from the technique.^{11 12}

In this study the technique caused no injury to the intraocular tissues at the low field strength (0.08 T) used and is considered to be safe. However, at the field strengths of more modern scanners it is likely to be too hazardous a technique to be a viable alternative to conventional x-ray, ultrasound, and CT scanning unless the magnetic properties of the foreign body are known.

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Retinal detachment in Axenfeld-Rieger syndrome

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SUMMARY Three cases of the association between the Axenfeld-Rieger syndrome and retinal detachment in one family are described. Serious damage to the posterior segment of the eye in the Axenfeld-Rieger syndrome has not previously been reported.

This study reports three cases from one family who had the Axenfeld-Rieger syndrome. They are particularly interesting because in addition to the characteristic clinical signs typical of this disorder they also have retinal detachment, in one case bilateral and in another with a giant tear. The young age at which the retinal detachment appeared in each case and the family history provided a basis for assuming that the detachment was probably hereditary. Our study of these cases raises the following question: Is it possible that the Axenfeld-Rieger syndrome is also a disease of the posterior segment of the eye?

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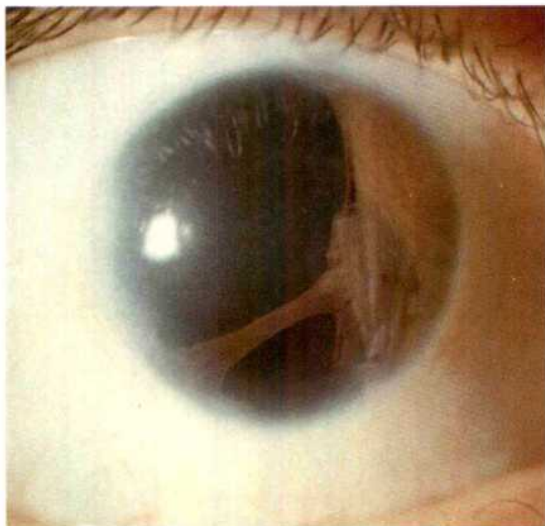


Fig. 1 Proband. Anterior segment of the right eye: partial aniridia from 7 to 12 o'clock with a full thickness hole in the inferior quadrant.

Case reports

CASE 1

The proband, a boy 14 years old, was referred to us for sudden blurred vision in his left eye. His parents were unrelated. His visual acuity was 0.1 in the right eye with -8 sph and counting fingers in the left eye with -9 sph. In the right eye ocular examination showed microcornea (8.5 mm) and partial aniridia from 7 to 12 o'clock, with a full thickness hole in the inferior quadrant (Fig. 1). Gonioscopic examination showed clearly a prominent Schwalbe's line and a band of transparent tissue attached to the peripheral cornea from the 3 to 4 o'clock position. From 8 to 12 o'clock iris processes were visible, and the iris was here present only as an iris root.

The patient had suffered from glaucoma for six years, and in fact even with topical therapy the ocular pressure in this eye was 32 mmHg. The right fundus showed a myopic crescent on the pale optic disc and an abrupt termination of the temporal retinal vascularisation at the equator.

External examination of the left eye showed a diagonal orientation of the ectopic pupil, with stromal iridic defects in the 3 o'clock position. The Schwalbe's anterior border ring was prominent from 3 to 9 o'clock. A small remnant of iris tissue was visible in the pupillary space (Fig. 2). Gonioscopic examination showed clearly the prominent Schwalbe's line, and iris processes were visible in the 6 o'clock position. Partial aniridia was present from 1 to 3 o'clock. Ocular pressure in the left eye was 5 mmHg. But the most unusual aspect was visible in the ocular fundus, which showed a retinal detachment with a giant tear extending for 270° from 9 to 6 o'clock (Fig. 3).

Non-ocular abnormalities consisted of a characteristic facial configuration with hypertelorism, flattening of the mid-face, a thin upper lip, and a protruding

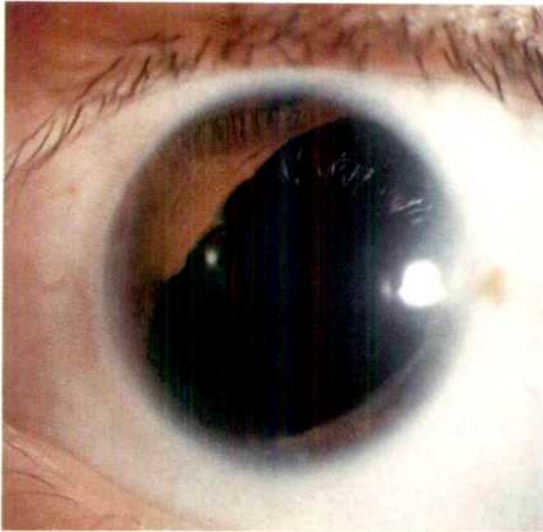


Fig. 2 Proband. Anterior segment of the left eye: diagonal orientation of the ectopic pupil, and a small remnant of pigmented iris tissue in the pupillary space.

lower lip. In addition microdontia, hypoplasia, and partial anodontia were present. The umbilicus was also very prominent. Since we considered this patient's ocular and non-ocular abnormalities to be typical of the Axenfeld-Rieger syndrome, we studied the family tree (Fig. 4).

CASE 2

A boy of 15, one of the brothers of the first patient, was also affected with the Axenfeld-Rieger syndrome. Six years earlier he had had a non-traumatic retinal detachment in his left eye. In the right eye visual acuity was 0.2 with -7 sph, and in the left eye was no perception light. External examination of the right

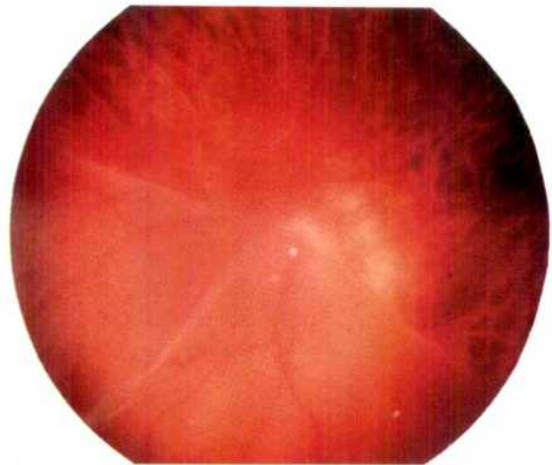


Fig. 3 Proband. Left eye: retinal detachment with giant tear.

eye showed corectopia and iridic atrophy, with the formation of holes in the quadrant opposite the direction of the pupillary displacement. Gonioscopic examination showed a prominent Schwalbe's line over 360°, and iris processes were visible from 7 to 11 o'clock. The ocular pressure in this eye was 40 mmHg with topical therapy. The ocular fundus showed a small pale optic disc with a large staphyloma, lacquer cracks, and haemorrhagic dots in the posterior pole.

The left eye was microphthalmic, and external examination showed a marked band keratopathy and a complete cataract that prevented gonioscopic and ocular fundus examinations. Echography showed a complete retinal detachment with proliferative vitreoretinopathy.

Non-ocular abnormalities were characterised by a typical facial configuration with hypertelorism, flat-

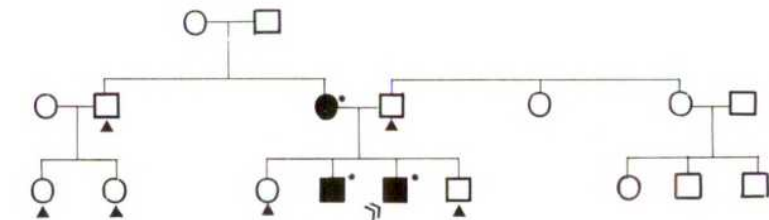
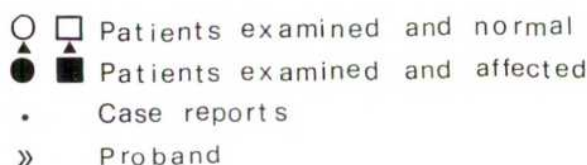


Fig. 4 Family tree of patients reported here.



tening of the mid-face, a thin upper lip with a long philtrum, and a receding chin. In addition there were a submucose palate, microdontia, anodontia, and an abnormal configuration of the teeth, which had a conical aspect. In this patient too the umbilicus was very prominent.

CASE 3

A woman 37 years old, mother of cases 1 and 2, is now completely blind as a result of bilateral retinal detachment. External examination of both eyes showed a dense band keratopathy with a complete cataract. The characteristic changes of the cornea, angle chamber, and iris were not visible owing to the cataract and corneal opacity. The ocular pressure was 10 mmHg in the right eye and 6 mmHg in the left eye. Her visual acuity, before bilateral retinal detachment, had been very poor with -5 sph in both eyes. In addition from the age of 12 she had suffered from bilateral glaucoma. Fifteen years before being seen she had had her first retinal detachment in the right eye. The patient thought this had a traumatic origin. The detachment was considered inoperable. The retinal detachment in her left eye had occurred seven years earlier and was non-traumatic. After two operations, however, the retina was still unattached. This eye is now microphthalmic, with corneal leukoma and cataract. The ecographic examination confirmed retinal detachment in both eyes, with proliferative vitreoretinopathy.

Non-ocular lesions in this patient were cleft palate, typical facial configuration, anodontia, and complete absence of finger nails and toe nails from birth.

Her other son and the daughter had no ocular or non-ocular abnormalities, and all the other members of the family examined were completely normal (Fig. 4). No consanguinity was present in the family tree.

Discussion

The occurrence of iris strands in addition to a prominent Schwalbe's line has traditionally been called Axenfeld's anomaly. If glaucoma is also present, the condition is known as Axenfeld's syndrome. Rieger¹⁻⁴ reported some cases with similar anterior segment anomalies but with additional changes, such as microcornea, corectopia, and atrophy and hole formation in the iris, and also some non-ocular abnormalities, especially of the teeth and facial bones. Rieger recognised that this disorder probably had an autosomal mode of inheritance. Subsequently some authors^{5,6} reported numerous patients with different combinations of the typical features of both the Axenfeld and the Rieger syndromes, even within the same family trees. The occurrence of the different lesions and also

the serious nature of the ocular and non-ocular anomalies varied considerably among members of the same pedigrees.⁷⁻¹¹ For this reason some authors now prefer to consider these two conditions within a single diagnostic category indicated by the general term Axenfeld-Rieger syndrome.¹²

This interesting defect is relatively rare. Many hypotheses^{3,12,13} have been proposed for its pathogenesis on the assumption that the lesions have a common developmental origin during embryonic life. All the embryologic hypotheses are based on the observation that the syndrome has been reported as involving only the anterior segment of the eye. Now in contrast we report here three cases from one family that in addition to the characteristic ocular and non-ocular signs, including anomalies of the anterior segment of the eye, also show serious impairment in the posterior segment, with retinal detachment (in one case bilateral) and in one case a giant retinal tear. In our opinion the retinal detachment in our patients is not related only to the high myopia present. In fact the young age at which it occurred and the family history suggest a hereditary origin for the detachment.

Other authors¹⁴⁻¹⁸ have described an association between the Rieger anomaly and certain developmental disorders. However, it is important to note that the developmental disorders were in non-ocular organs. The Axenfeld-Rieger syndrome comprises a range of ocular and non-ocular development disorders which may occur differently within the same family tree, and all the syndromes characterised by an association between ocular and non-ocular abnormalities caused by an arrest of development of some embryonic cells are not always so clear-cut as the traditional classifications would imply.¹⁹ It is possible that failure in the development of embryonic cells and consequent alteration of their interactions with adjacent tissue may lead to the ocular and non-ocular anomalies of the Axenfeld-Rieger syndrome and may also generate posterior segment disorders, which perhaps are the cause of retinal detachment in our young patients.

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Effect of cataract extraction on the pupil response to mydriatics

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SUMMARY Pupil diameters in the dark, in the light, and after mydriasis with tropicamide+phenylephrine have been measured in 25 patients before and six months after cataract surgery. The aphakic pupil showed reduced mobility as evidenced by a smaller diameter in the dark and a larger one in the light. In patients who had intracapsular extraction or extracapsular extraction with intraocular lens implantation the pupils dilated less well than preoperatively. The difference in response to mydriatics is of practical importance in the assessment and treatment of peripheral retinal disorders in aphakic and pseudophakic eyes.

It is a clinical impression that aphakic eyes do not dilate as well as phakic eyes to the topical application of mydriatics, so that the view of, and access to, the peripheral fundus is limited. The aim of this study was to test this impression. The investigation was conducted at a time when both intracapsular cataract extractions (ICCE) and extracapsular cataract extractions (ECCE) were being conducted routinely, with and without intraocular lens (IOL) implantation.

Patients and methods

Twenty-five patients (10 male, 15 female), aged 46-84 years, were recruited to the study. None was diabetic or receiving medication which might affect function in the autonomic nervous system. Each attended on two occasions, immediately before and approximately six months after cataract extraction.

At each attendance the pupil diameters were measured in the dark and under bright continuous illumination by infrared television pupillography.¹ This illumination, from two fluorescent lamps placed 50 cm from the patient, was of a brightness comparable to that needed for ophthalmic practice. Pupils were measured before and 60 min after application of mydriatic eyedrops (1 drop of each drug bilaterally): tropicamide 0.5% and phenylephrine 10% (Minims, Smith and Nephew Pharmaceuticals). Mydriatics

were not instilled postoperatively into the eyes of one patient who had an iris-supported lens implanted.

Some data were not obtainable where: (1) the cataract was sufficiently white to preclude pupillographic measurements (in which good pupil/iris contrast is crucial); (2) the diameter of the pupil was too small to register (<1.9 mm); (3) light reflection from the cornea obscured the view.

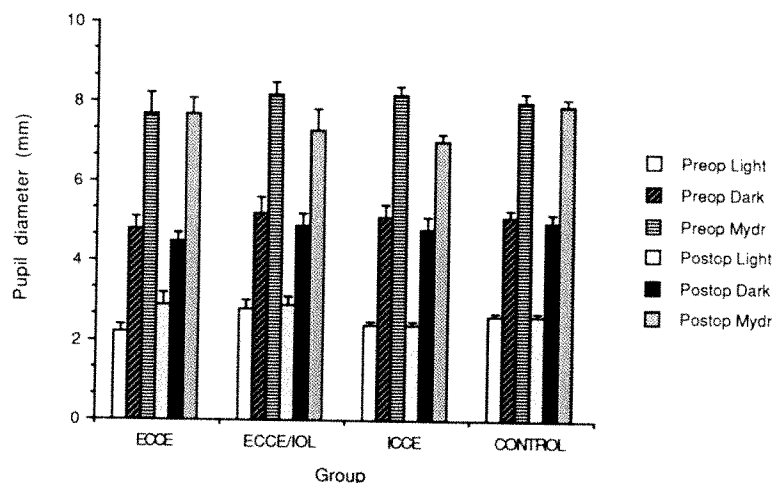
The results of the experiment were assessed only where paired comparisons (postoperative versus preoperative) could be made; they were evaluated by Student's paired *t* tests by standard methods. The study was approved by the Ethics Committee of West Lambeth Health Authority.

Results

Sixteen of the 25 patients, aged 70.6 (2.4) yr (mean, SEM), underwent ECCEs, seven of these with posterior chamber IOL implantation. Nine patients aged 67.2 (3.2) yr underwent ICCEs, none with IOL implant. Twelve patients received peripheral iridectomies. The operations were carried out by several different surgeons. None of the postoperative eyes showed evidence of posterior synechiae, peripheral anterior synechiae, iris root adhesions to the incision, vitreous or capsule strands to the incision, or pupil capture, any of which complications might have resulted in impaired iris mobility.^{2,5}

Fig. 1 shows the mean pupil diameters of the operated and the fellow eyes in both darkness and

Fig. 1 Pupil diameters (mean $\pm$ SEM) in the dark, in the light, and following application of mydriatics in patients before and after ECCE (extracapsular cataract extraction without intraocular lens implant, 9 eyes), ECCE/IOL (extracapsular cataract extraction with intraocular lens implant, 7 eyes), ICCE (intracapsular cataract extraction without lens implant, 9 eyes), and CONTROL (unoperated, 22 eyes).



bright illumination before mydriasis and 60 min after application of mydriatics. At this latter stage for all eyes the mean change in diameter with the bright illumination was less than 0.01 mm, indicating that the light reflex had been totally abolished. There was no significant difference between the preoperative pupil diameters of the eyes which subsequently underwent the three operative procedures.

The resting diameter in the dark of the aphakic eyes was 0.3 mm smaller than preoperatively ($p < 0.0025$), whereas that in the fellow control eyes was unchanged. By contrast under bright illumination the resting diameter of the aphakic eye was 0.3 mm larger than before surgery ($p < 0.01$), whereas that of the fellow eyes was unchanged. Cataract extraction was therefore associated with a small reduction in iris mobility.

The final diameter of the aphakic and pseudophakic eyes after mydriasis was 0.7 mm less than preoperatively ($p < 0.0025$), whereas in the fellow control eyes there was no change. The final diameter after mydriasis of the nine eyes which had undergone ECCE without IOL implantation was not significantly different from preoperatively. With posterior chamber IOL implantation (seven eyes), however, the final diameter after mydriasis was 0.9 mm smaller than preoperatively ($p < 0.02$). Similarly, in the nine eyes which had undergone ICCE the diameter after mydriasis was 1.2 mm smaller than preoperatively ($p < 0.02$). Among these affected groups three out of 16 patients' pupils dilated to final diameters of 6 mm or less.

Discussion

This study has shown that in the dark the resting aphakic pupil is smaller than preoperatively but that

in the light it constricts less. Furthermore the aphakic pupil responds less to mydriatics, reaching a smaller final diameter than preoperatively. In three of our cases the pupils did not dilate beyond 6 mm, a size which is critically small for examination or treatment of the peripheral retina.

The explanation for these findings probably lies with the amount of iris trauma occurring at operation.⁴ Damage to the sphincter pupillae will result in a reduced ability of the iris to constrict in response to light. Conversely, damage to dilator fibres will reduce the response to mydriatic drugs. This series suggests that the amount of iris trauma, as indicated by poor response to mydriatics, was greatest for ICCEs, followed by ECCEs with IOLs, and least for ECCEs alone.

Eyes undergoing ECCE alone showed little change between preoperative and postoperative mydriatic response, which suggests that nucleus expression and soft lens matter aspiration causes little direct iris trauma. Greater trauma is understandably caused by the implantation of a posterior chamber IOL. Since this study was conducted at a time when some surgeons were converting from ICCEs to ECCEs with IOLs, it is likely that this degree of trauma will be further lessened by improved skills, techniques, lens design, and instrumentation.

All the ICCEs underwent peripheral iridectomy, which of necessity causes direct iris trauma. This probably accounts for the poorer response to mydriatics in this group. Since to omit the peripheral iridectomy would increase the risk of pupil-block glaucoma,⁶ decreased pupil mobility must be considered the inevitable response to intracapsular surgery. The risk of retinal detachment following cataract surgery is up to 2%⁷ and is greater following intracapsular than extracapsular surgery.⁸ The

poorer ability of the former cases to respond to mydriatics may in practice compound the problem.

In conclusion, the study confirms the clinical impression that aphakic and pseudophakic pupils dilate less well than phakic pupils. This may be of considerable relevance when attempting to examine or treat the peripheral retina of the aphakic eye, especially following intracapsular cataract extraction.

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A film video processor for the viewing of fluorescein angiograms

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SUMMARY A new, commercially available, and inexpensive film video processor facilitates the viewing of fluorescein angiograms on video monitors. The negative film is inserted into a film carrier, read by a charge-coupled device solid state pickup device and presented as a negative or positive image on a black-and-white monitor with the help of a negative/positive conversion feature. Details of the angiogram are studied by zooming into any part of the image, which magnifies the image up to six times. Contrast and brightness adjustment on the video monitor allows examination of under- or overexposed angiograms.

Fluorescein angiograms are usually examined with the help of loupes, microfilm readers, or slide projectors.^{1,2} Despite the fact that the negative film provides more details, many ophthalmologists prefer to study positive images of the angiogram obtained by contact printing on a sheet of transparent film, a procedure which takes time and increases the expense considerably. The presentation of positive images of angiograms on video screens would reduce considerably the cost of production of the positive image as well as the time until the angiogram can be

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evaluated. A custom-made closed-circuit television system, which can also be used for the presentation of fluorescein angiograms, was presented recently.³ We tested a new, commercially available, and inexpensive film video processor in order to evaluate its qualification for the presentation of fluorescein angiograms.

Material and methods

The Tamron Fotovix film video processor (Tamron Co., Omiya Saitama, Japan) is a small, compact (width×height×depth: 190×230×350 mm) and light

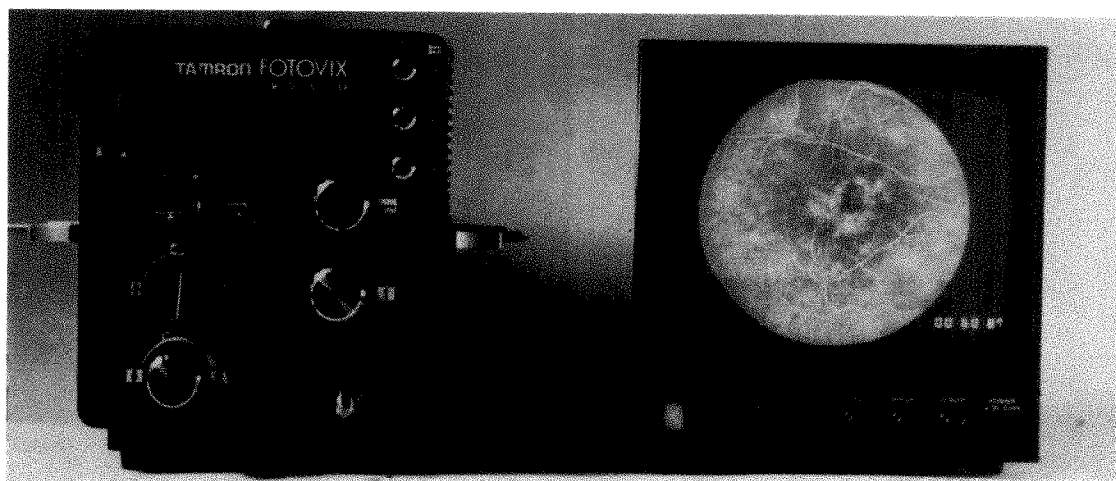


Fig. 1 Fotovix film video processor connected to a 9-inch (22.9 cm) black-and-white monitor.

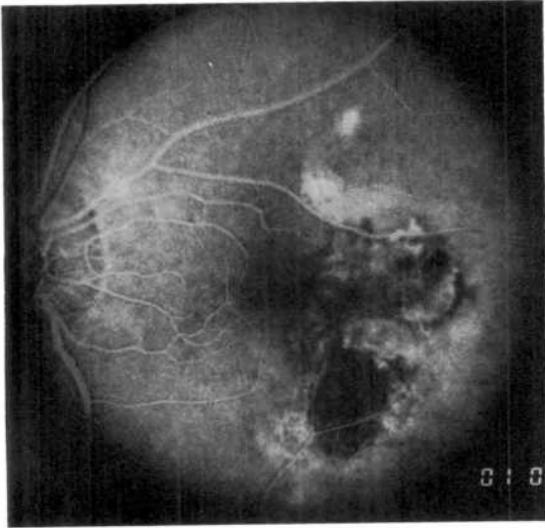


Fig. 2 Conventional print of a fluorescein angiogram showing a parafoveal subretinal neovascular membrane adjacent to a chorioretinal scar caused by ocular toxoplasmosis.

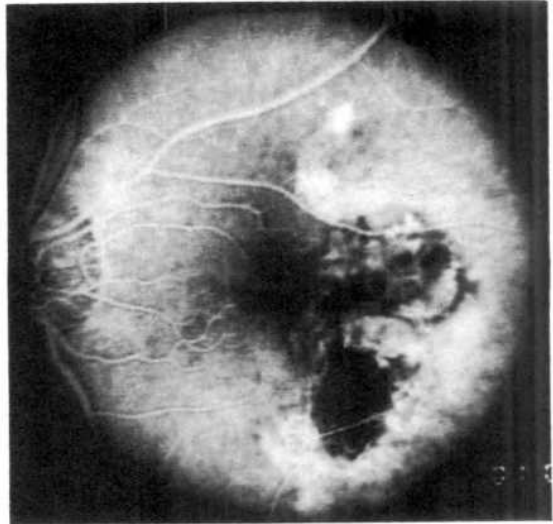


Fig. 3 Screen shot (full-frame mode) of the same frame as Fig. 2. Owing to the low resolution the image seems blurred, and the perifoveal capillaries are almost invisible.

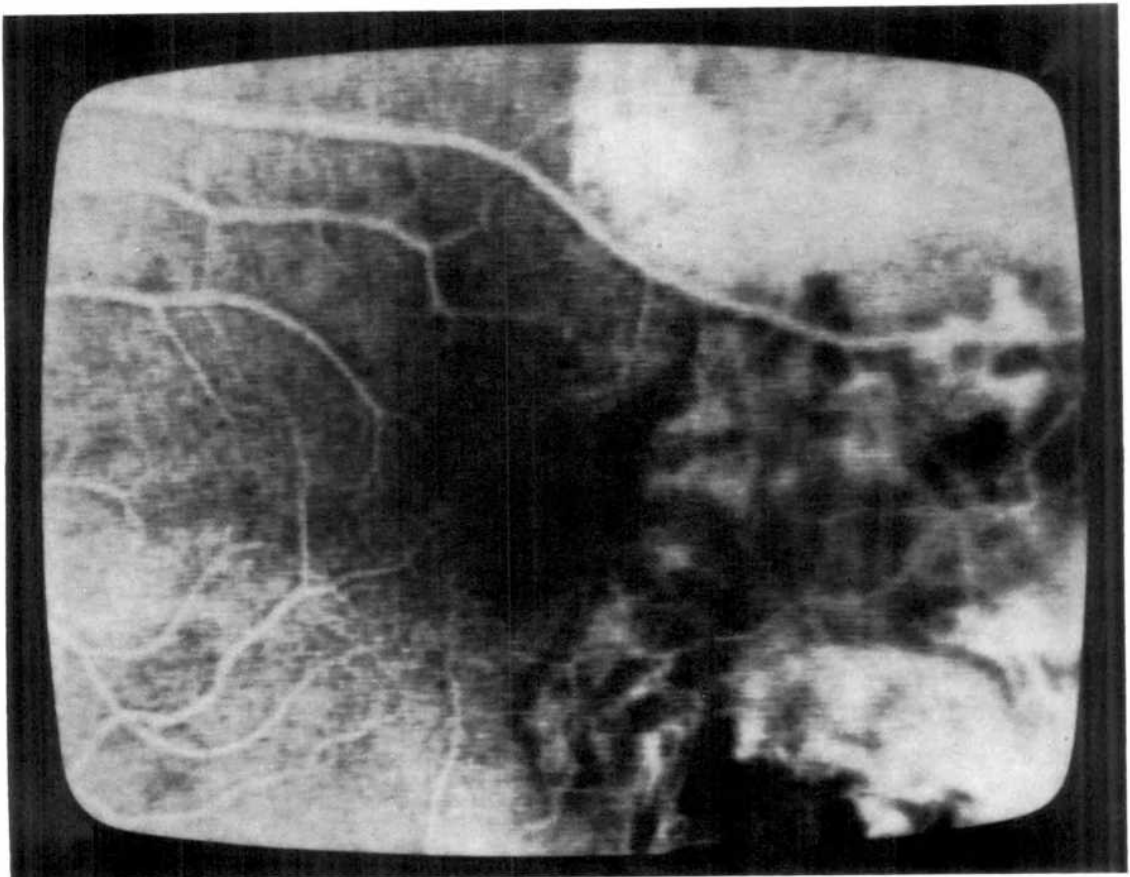


Fig. 4 Screen shot of part of the frame of Figs. 2 and 3. The image shows more detail than Fig. 3; the perifoveal capillaries are visible. $\times 2$.

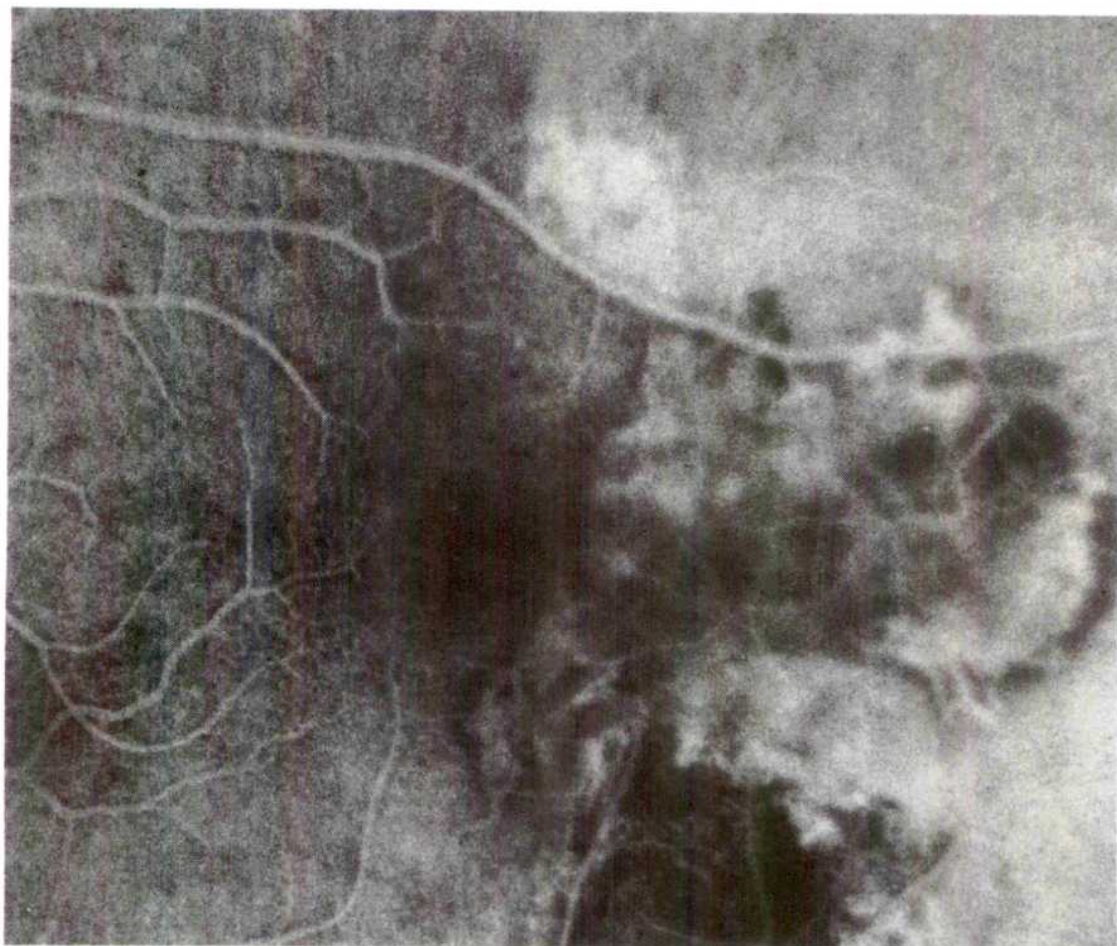


Fig. 5 Conventional print with the same magnification as Fig. 4. Owing to the limits of the film resolution the difference from Fig. 4 is not significant.

weight (6 kg) unit which contains a stage for 35 mm film or slide carriers, a charge-coupled device (CCD) solid state colour pickup device with a zoom lens, an illumination system, a negative/positive conversion feature, and controls for horizontal and vertical adjustment, focus, brightness, and colour (Fig. 1). The film carrier is large enough to hold a 35 mm negative film strip with six frames. Two video output pinjacks, one for colour and one for monochrome, and a radio frequency adapter output are available. We connected a Sony PVM-91CE black-and-white monitor (Sony Co., Japan) to the monochrome video output.

Results

The quality of the video image was sufficient for evaluation of fluorescein angiograms. When the full

frame is presented, small details are not as clearly visible as on a conventional positive print (Figs. 2, 3). Nevertheless the shortcomings of the low resolution of the CCD pickup device might be compensated for with the help of the zooming feature (Fig. 4). The adjustment of the magnification of the image permits a minute examination of the angiogram, and the viewing of several sequential frames is assisted by the horizontal positioning control. Under- or over-exposed angiograms may also be examined without difficulty, as the Fotovix performs an automated adjustment of image brightness, which can be fine-tuned with the brightness and contrast controls of the video monitor.

Discussion

The evaluation of fluorescein angiograms has gained

importance because of the increasing frequency of laser treatment for macular diseases. The treatment of a subretinal neovascular membrane requires a recent angiogram, which should be compared with the biomicroscopic findings during the laser treatment procedure.² A single frame of negative or positive film, however, may be inadequate to show subtle details, which are often visible only after comparison of sequential frames. Thus the Fotovix film video processor, which presents the negative or positive image of sequential frames of an angiogram at a preselected magnification, may be able to replace conventional presentation devices even in spite of its shortcomings. Other advantages of the film video processor are the low cost of operation, which might pay off the cost of purchase (price: US\$ 2198) within a few months, and the possibility of using it for demonstration and teaching. The combination of conventional fluorescein angiography with film video processing and presentation of the angiogram on a video screen is also less expensive than video angiography, which still cannot provide the high resolution of modern 400 ASA black-and-white negative film.

The main disadvantages of the film video processor are the absence of the possibility of a stereoscopic examination and the low resolution in full-frame

mode, which prevents the use of the video signal for digital image processing. These disadvantages, however, are of minor importance, since the negative film is still available for stereoscopic examination, printing, or scanning into an image processing system if necessary. Thus the film video processor Fotovix may be recommended for the examination of fluorescein angiograms during laser treatment of macular diseases and for the presentation of angiograms to a larger audience.

This study was supported in part by the Austrian Fund for the Propagation of Scientific Research (Österreichischer Fonds zur Förderung der wissenschaftlichen Forschung, P 5789).

The author has no direct or indirect proprietary interest in this device.

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Validation of a photographic method of measuring corneal diameter

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SUMMARY A photographic method for measuring corneal diameter using the Medical-Nikkor f 200 mm lens is described. Measurements were compared with those obtained by calipers (46 eyes of 25 patients) and by placing a ruler either near the eye (123 eyes of 64 patients) or on the nose (98 eyes of 55 patients). Over all we found good correlation between photographic and caliper measurements ($r=0.94$). No significant correlation was found between photographic measurements and estimates made with the ruler either near the eye or on the nose ($r=0.65$ and 0.31 respectively). Modifications to our system are suggested which may provide an accurate, simple, non-invasive method of measuring corneal diameter in ophthalmic clinics.

The measurement of corneal diameter is an essential part of monitoring the progress of congenital glaucoma during infancy and early childhood. It is also of value in quantifying corneal size in congenital or acquired anomalies of the globe and in quantifying corneal growth.

Three methods of measurement are available: first, by placing a ruler near the eye; secondly, a direct caliper reading from the cornea; thirdly, by using a slit-lamp attachment. For infants and young children neither the second nor third methods are generally applicable.

There have been several reports of previous attempts to develop an alternative to the use of calipers for measurement of corneal size.¹⁻³ Both Aizawa and co-workers¹ and Kikkawa² employed photographic techniques. The former used a fixed focus camera and measured the corneal diameters in 40 children (up to 6 years) but did not compare their results directly with values obtained by standard techniques. Kikkawa used a camera of variable focus to photograph both the eye and a plastic ruler to provide a permanent record for the notes.

This series of experiments was designed to validate the use of a photographic technique, which could

provide a simple non-invasive method of monitoring corneal diameter while also providing a permanent record for follow-up of cases.

Patients and methods

APPARATUS

A Medical-Nikkor f 200 mm lens attached to a Nikon F1 camera back was used to obtain photographic records of the eye. The Medical-Nikkor Auto 200 mm f/5.6 lens was designed for taking close up photographs of known reproduction ratio with the minimum of time and trouble. It is a fixed focus lens with a reproduction ratio of 1:15. Use of an auxiliary lens altered this ratio to 1:1. Focusing is achieved simply by pointing the camera at the eye and moving it back and forth until the eye is in sharp focus. The output of the ring flash was filtered by a combination of EE and 30 CC Blue filters (Kodak Wratten), which effectively block all UV light emitted by the flash.

Fast film (Kodak TMX Professional, ASA 400) was loaded so that the exposure duration could be kept to a minimum. An aperture of f 32, which in combination with the $\times 1$ auxiliary lens produces a depth of field of ± 1.86 mm* that is the eye was only in focus when the distance lens to eye was in the range 219.14 to 222.86 mm. The lens to subject distance was 221 mm with this combination of lenses, and the subject field was 24 by 36 mm.

*Information supplied by Nikkon, UK Ltd, and confirmed by a series of preliminary experiments.

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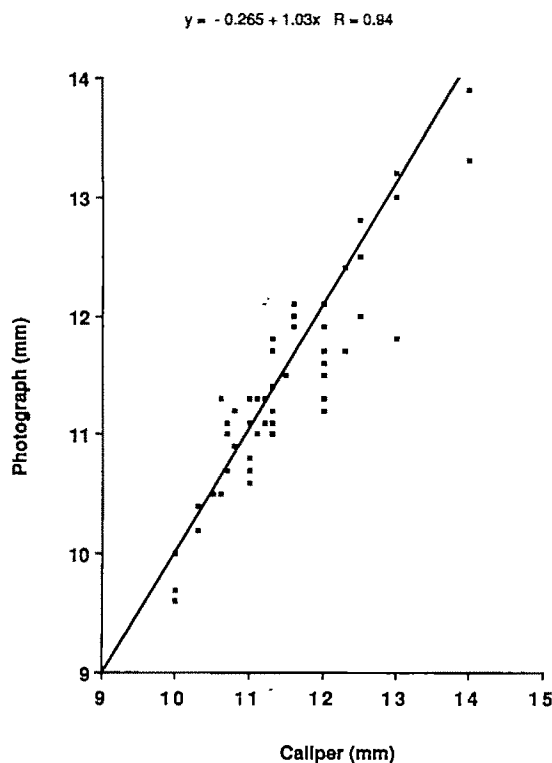


Fig. 1 Scattergram and linear regression for the photographic corneal diameter measurements compared with the caliper measurements. Solid line, regression line of photographic measurement on caliper measurement ($y = -0.265 + 1.03x$ with $r = 0.94$).

PATIENTS

Comparison of photographic and caliper measurements. Paediatric and adult patients (46 eyes from 25 patients) undergoing ophthalmic surgery were examined in this part of the study. Measurements were taken while they were under general anaesthesia and prior to commencing the procedure. A photograph was taken, and a second investigator then measured both the horizontal and vertical corneal diameters (white-to-white) using a caliper and ruler.

Comparison of photographic with ruler measurements. Corneal diameters of patients attending the Ophthalmic Department of the Leicester Royal Infirmary were measured with a plastic ruler by an ophthalmologist. Each eye was subsequently photographed by a second investigator. Two series of records were made: in the first the ruler was positioned on the patient's nose (123 eyes from 64 patients), and in the second the ruler was placed near the eye (98 eyes from 55 patients).

Measurement of corneal diameters from photo-

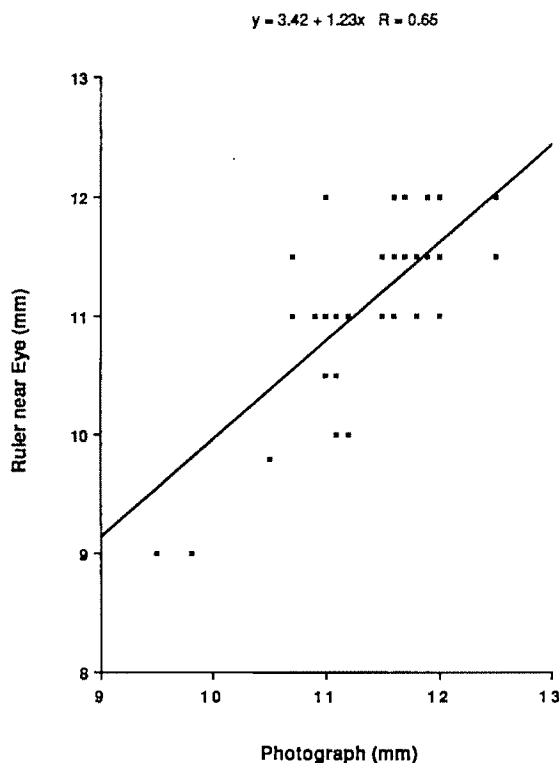


Fig. 2 Scattergram and linear regression for the photographic corneal diameter measurements compared with measurements made with the ruler near the eye. Solid line indicates the regression line of ruler measurement on photographic measurement ($y = 3.42 + 1.23x$ with $r = 0.65$).

graphic records. Films were processed by a modification of the fluorescein process to minimise grain size on the negatives. Two observers then independently measured the horizontal and vertical visible iris diameters directly from the negatives using a magnifying scale lens (peak scale loupe $\times 7$).

ANALYSIS OF RESULTS

Correlation coefficients, Student's paired t test, and analysis of least squares were used to analyse the statistical significance of the data. Because measurements were carried out on right and left eyes, there may be some interdependence of measurements of the data. However, any such interdependence of measurements of right and left eyes was not expected to interfere critically with the design of the study. Therefore we treated the measurements of both eyes independently in the statistical analysis.

Results

There was good overall correlation between the

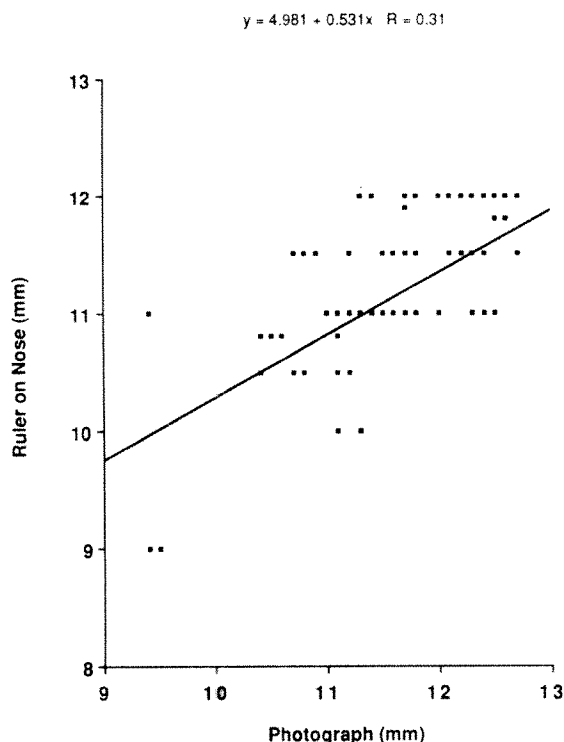


Fig. 3 Scattergram and linear regression for the photographic corneal diameter measurements compared with measurements made with the ruler on the nose. Solid line indicates the regression line of ruler measurement on photographic measurement ($y = 4.98 + 0.53x$ with $r = 0.31$).

caliper and photographic methods ($r = 0.94$). The deviation from zero correlation was tested by a paired t test ($t = 2.04$), which was not significant at the 0.05 level with $n - 2$ degrees of freedom. Fig. 1 shows a scattergram and linear regression for the photographic corneal diameters compared with the caliper measurements. The linear regression line was:

$$\text{Photo} = -0.265 + 1.03 \text{ caliper.}$$

The standard error of estimate of this linear regression was 0.07 mm.

This analysis showed that there were no significant differences between the estimates of corneal diameter obtained from calipers or photographs ($F = 204.271$, $p < 0.0001$). Good interobserver agreement was noted ($r = 0.97$) between measurements of corneal diameter obtained from the photographic records.

When the photographic estimates were compared with those obtained by a plastic ruler placed near the eye (Fig. 2) or on the patient's nose (Fig. 3) no significant correlation was noted ($r = 0.65$ and $r = 0.31$ respectively).

Discussion

These results show that caliper and photographic measurements of corneal diameter correlate well. Photographs have several advantages over both caliper and ruler measurements. Firstly, they are simple to perform and do not require the use of a general or topical anaesthetic. Secondly, they provide a permanent record which may be of practical use in monitoring the progress of certain ocular conditions.² Finally, the photographic method is more accurate: diameters may be measured to the nearest 0.05 mm from the photographs compared with ± 0.25 mm with calipers or ± 0.5 mm with a ruler. A further unknown aspect is observer bias, as most adult corneal diameters fall within a known narrow range. The ruler 'measurement' is the combination of this ruler finding and qualitative clinical assessment. In the absence of this last clue it is probable that ruler measurements would show considerably more variation.

At present when the corneal diameter is measured in an infant or child clinic it is estimated by placing a ruler near the eye. Not surprisingly our results suggest that the positioning of the ruler affects the estimate of cornea size (see Figs. 2 and 3). Perhaps parallax errors may explain low correlations found between measurements taken when the ruler was placed on the nose and photographic estimates. However, on this principle we would have expected ruler measurements to have consistently overestimated those obtained photographically, and this was not the case.

The question remains as to the practical implication of these findings for the clinical measurement of corneal diameters. Slight modifications to the photographic system which was used in this research could provide a simple non-invasive method of measuring corneal size. One option would be the use of Polaroid film; together with adaptor rings it may be possible to attach the Medical-Nikkor lens to a substitute camera back. Alternatively, use of the magnifying lens could be avoided by loading a technical film (preprinted with a scale), though such films must be processed in the standard way.

Knowledge of corneal size can be useful in a variety of clinical circumstances, including the management of congenital glaucoma and, in the adult, when trying to ascertain whether the pathological process was of early onset or after the first year of life and completion of corneal growth. This technique also has considerable potential in the study of corneal growth.

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Ceftriaxone diffusion from blood to aqueous humour in man

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SUMMARY Ceftriaxone penetrates into the aqueous humour in man. The interaction of indomethacin on the disposition of ceftriaxone appeared to be time-dependent. Indomethacin delayed ceftriaxone penetration into, but enhanced its persistence in, the aqueous humour, permitting a period of antibioprophylaxis covering the required time for surgical treatment.

Ceftriaxone (Rocephin), a third generation cephalosporin, is widely used in ophthalmological surgery to prevent postoperative infections. It is active against a wide variety of pathogens, and its long terminal half-life permits a single preoperative intravenous administration. Although highly protein-bound (more than 90%), ceftriaxone shows good penetration of cerebrospinal fluid and eye.^{1,2} It is well known that indomethacin, a prostaglandin synthesis inhibitor, interacts with several drugs—epinephrine, ceftazidime, timolol.³⁻⁵ In this trial we studied the intraocular kinetics of ceftriaxone and the influence of indomethacin administration.

Patients and methods

Forty eight patients, 15 male and 33 female, ranging in age from 28 to 89 years (mean 72, SD 11), who had had cataract extractions were included in this study. They had no history of allergy to β -lactam antibiotics. All the operated eyes were free from infection and inflammation. The patients received 2 g of ceftriaxone during a 10-minute infusion. They were divided into two groups of 24 each. Group 1 received ceftriaxone alone, group 2 ceftriaxone and intrarectal indomethacin (100 mg) the day before surgery. Local anaesthesia was with a lidocaine-etidocaine mixture, and sedation was by flunitrazepam and phenerperidin.

Biochemical tests on all the patients gave normal results and protein levels were within the normal range. Blood and aqueous humour (0.1 ml collected

by anterior chamber paracentesis) samples were collected 30 minutes, and 1, 2, and 3 hours after the end of ceftriaxone infusion from six patients at each time for each group. Blood samples were centrifuged after collection, and plasma was removed and stored with aqueous humour (AH) at -20°C before assay. The samples were assayed by specific high liquid performance chromatography.⁶

Data were compared by Student's *t* test and were expressed as mean and SE of mean.

Results

The concentrations of ceftriaxone in plasma and aqueous humour are shown in Tables 1 and 2 for the two groups of patients. The ceftriaxone plasma levels obtained in both groups of patients were in the same range as those reported.⁶

The penetration kinetics of ceftriaxone in aqueous humour were faster in group 1 than in group 2. Furthermore, we found a statistical difference between the two groups for plasma and aqueous humour ceftriaxone levels two hours after the end of

Table 1 Ceftriaxone plasma concentrations: ceftriaxone alone (CA) and ceftriaxone plus indomethacin (CI)

Time (hour)	Plasma $\mu\text{g/ml}$ CA	Plasma $\mu\text{g/ml}$ CI
0.5	215 (36)	193 (38) NS
1.0	205 (41)	176 (15) NS
2.0	194 (19)	158 (18) S
3.0	152 (21)	154 (18) NS

Each value is the mean (SE) for six patients. NS=not significant. S=significant ($p<0.01$).

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Table 2 Ceftriaxone aqueous humour concentrations: ceftriaxone alone (CA) and ceftriaxone plus indomethacin (CI)

Time (hour)	Aqueous humour µg/ml CA	Aqueous humour µg/ml CI
0.5	ND	ND
1.0	6.0 (3.2)	ND
2.0	1.0 (0.7)	3.1 (2.2) S
3.0	ND	2.1 (4.2) S

Each value is the mean (SE) for six patients. ND=below limit of detection. NS=not significant. S=significant ($p<0.01$).

the antibiotic infusions: higher plasma concentrations and lower aqueous humour levels in group 1 and the contrary for group 2. Three hours after infusion the statistical difference was only in the aqueous humour.

Discussion

The spectrum of ceftriaxone is similar to that of the other cephalosporins. The main difference is its long plasma half-life.⁷ It is well known that ceftriaxone crosses the blood-brain and blood-ocular barriers, and prolonged aqueous humour levels are probably related to its prolonged plasma levels.²

Indomethacin seems to interfere with ceftriaxone. This interference involves ceftriaxone plasma and aqueous humour kinetics (levels and persistence).

The synergistic influence of both drugs is interest-

ing because it permits a longer antibioprophyllaxis for anterior chamber surgery. Furthermore indomethacin, either systemic or topical, may have a protective effect against cystoid macular oedema following cataract extraction.⁸

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Eyelid swelling and erythema as the only signs of subperiosteal abscess

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SUMMARY On clinical grounds it is usually easy to distinguish between preseptal cellulitis, a cutaneous infection not threatening to vision, and orbital cellulitis, a potentially vision threatening infection of the orbital tissues generally arising from paranasal sinusitis. We recently cared for two patients with a clinical diagnosis of preseptal cellulitis who had CT scan evidence of subperiosteal abscess. Antibiotic therapy alone resulted in clinical resolution in each case.

Unilateral erythema and oedema of the eyelids unassociated with proptosis, conjunctival injection and chemosis, restricted motility, and diminished vision comprise the clinical diagnosis of preseptal cellulitis.¹ Radiological examination in such cases is infrequent, and empirical treatment with oral antibiotics on an ambulatory basis is often begun. More serious involvement of posterior structures (orbital

cellulitis), generally requiring intravenous therapy with admission to hospital, is usually indicated by proptosis, restricted motility, and/or visual dysfunction.¹

We report on two patients with radiographic evidence of ethmoidal sinusitis and subperiosteal orbital abscess in whom eyelid swelling and erythema were the only clinical signs.

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Case reports

CASE 1

A 4-year-old boy was well until he sustained unobserved (and presumed minor) trauma to his right eye. He developed transient conjunctival injection, which abated within 24 hours. One day later erythema and oedema of the right eyelids ensued. There was no accompanying fever or ocular pain.

Ophthalmic examination showed visual acuity of 6/9 (Allen pictures) in each eye. There was moderate oedema and slight erythema of the right upper and lower eyelids (Fig. 1). No chemosis or conjunctival injection was noted. The pupils were normal, with no afferent pupil defect. There was no proptosis or resistance to retropulsion of the globe. Extraocular movements were full, and he was orthophoric in primary gaze. Funduscopy examination showed nothing abnormal, and no choroidal folds were seen. The child was afebrile, and the general physical examination gave normal results.



Fig. 1 Case 1. Note the marked oedema of upper and lower left eyelids.

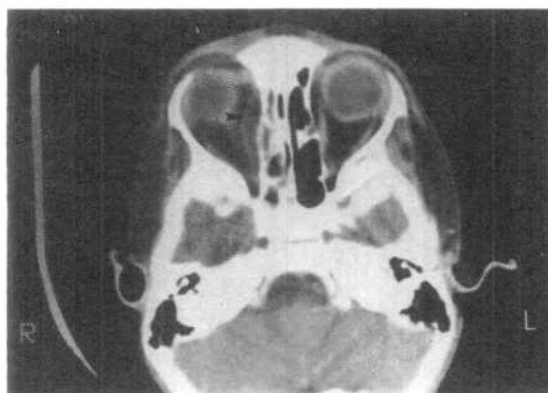


Fig. 2 Case 1. Computed axial tomography of the orbits showing subperiosteal elevation and lateral displacement of the medial rectus muscle (arrowhead).

Orbital computed tomography (CT) showed right ethmoidal sinusitis and a subperiosteal density with lateral displacement and enlargement of the medial rectus muscle (Fig. 2). No orbital fractures were identified. Intravenous antibiotic therapy (nafcillin and chloramphenicol) was instituted, and complete resolution of clinical signs was noted within one week. A follow-up CT scan performed two weeks later was normal.

CASE 2

A 7½-year-old boy had a four-day history of redness and swelling of his left eyelids accompanied by a left frontal headache. He experienced no change in his usual pattern of nasal discharge from chronic allergic rhinitis.

The boy was afebrile. His visual acuity was 6/6 and



Fig. 3 Case 2. Preseptal oedema and erythema without conjunctival injection.

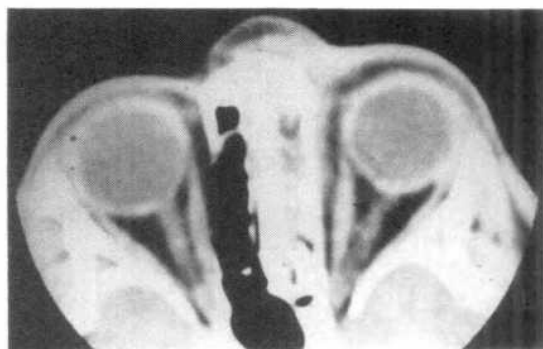


Fig. 4 Case 2. Computed axial tomography of the orbits showing ethmoid sinusitis and enlargement and lateral displacement of the left medial rectus muscle (arrowhead).

6/7.5 in the right and left eyes respectively. The left periorbital region was erythematous to the boundary of the orbital septum (Fig. 3). His pupils reacted normally, with no afferent pupillary defect. There was no strabismus, restricted motility, or proptosis, and no conjunctival injection or chemosis. Funduscopic examination gave normal results. CT scan revealed thickening of the periosteum on the left and bulging of the left medial rectus muscle into the muscle cone (Fig. 4).

The patient was treated with intravenous nafcillin and chloramphenicol for seven days and had complete clinical and radiological recovery.

Discussion

Isolated eyelid swelling and erythema usually indicates primary infection anterior to the orbital septum (preseptal cellulitis) but may also be the first sign of an underlying frontal or ethmoidal sinusitis² (an association known better to otolaryngologists than ophthalmologists). While preseptal cellulitis (which usually results from minor trauma) may be treated with oral antibiotics on an ambulatory basis, orbital cellulitis and its subgroups, subperiosteal abscess and orbital abscess (which most often arise secondarily to an adjacent paranasal sinusitis), warrant more aggressive therapy with intravenous antibiotics and sometimes surgical intervention.^{3,4} The latter types of orbital infection are usually recognised because they produce proptosis and/or restricted motility.^{1,5} Unilateral, total, acute, irreversible visual loss was recently reported to occur in a patient on oral antibiotics with clinical paranasal sinusitis and isolated eyelid swelling as the only ophthalmic sign.⁶ None of the characteristic signs of orbital involvement were present (as in the two patients presented here). CT demonstrated spheno-

ethmoiditis, with no evident orbital pathology. Presumably an optic neuropathy in the orbital apex or in the optic canal, secondary to adjacent infection or inflammation, was the cause of visual loss.

We consider that the clinical syndrome of preseptal cellulitis may overlap orbital cellulitis with subperiosteal abscess. Radiological exclusion of underlying paranasal sinusitis with or without orbital involvement should be considered, especially in cases such as these in which minor trauma as a cause of preseptal cellulitis was absent (making the antecedent history atypical), or in cases where there is a history consistent with sinusitis. Appropriate therapy may then be instituted to ward off possible visual sequelae.

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Risk factors for cataract

SIR, It was with much interest that we read the recent reports by van Heyningen and Harding on risk factors for cataract.^{1,2} The authors should be congratulated on their work. However, as they had collected a data set of such quality, we were surprised that they did not present the results of two important analyses.

First, it seems clear that, while the aetiology of cataract is multifactorial, the risk factors for the three major different types of cataract (cortical, nuclear, and posterior subcapsular) are also very likely to be different. This being the case, the authors should be strongly encouraged to do a series of subanalyses for each predominant type of cataract, data they surely will have collected.

Second, with the advent of computerised data analysis, much more sophisticated methods of assessing the contribution of multiple risk factors are available. These methods include logistic and polychotomous regression models. The major advantage of the various regression models is that they can simultaneously control for the potential confounding effect of multiple factors that could be related or could interact. The use of these techniques enables the 'study of interactive factors', which in the present study was done on only a very limited scale because 'the numbers reporting any two specific factors are small'.¹ It would also avoid the artefact induced by excluding various subgroups—for example, those reporting steroids from the analysis of the effect of aspirin-like analgesics.² As the authors suggest, there may be a link between severe diarrhoea and military service (and therefore also place of work?), and it could be that these former servicemen also drank more beer and smoked more heavily. The simple stratification used by the authors did not resolve this issue and neither will an analysis of interaction that does not include all the relevant parameters that were identified by bivariate analysis. If the authors have undertaken a comprehensive multivariate analysis using either of the software packages they mention, they should present their results. If they have not, they should do so.

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SIR, We are grateful to Drs Taylor and Muñoz for their interest in our work and for their two suggestions. In response to the first: our aim was, as stated, to identify

major risk factors for cataract of any type.¹ In earlier studies such as that in Edinburgh the major morphological types of cataract were noted but have not resulted in the discovery of any entirely new risk factor.² Indeed most of the different types of cataract were highly correlated with each other, and although cuneiform cataracts were more weakly correlated than others they showed a major risk factor, diabetes, in common with other morphological types of cataract.³ Even though there was a small excess of cuneiform opacities in diabetics, almost 90% of such opacities were in non-diabetics. The correlation between different morphologies is a manifestation of the well-known occurrence of more than one type of opacity in many cataractous lenses.⁴ Furthermore each cataract patient may report several risk factors—a mean of four apiece in the Edinburgh study.² In the opposite sense a single risk factor, for example, diabetes, has been associated with a variety of different morphological types of cataract both in laboratory animals and in man. This and evidence of a multifactorial aetiology for cataract led to the view that there is a final common network of paths leading to cataract.⁵

Turning to their second point: there are highly sophisticated methods available for the study of multiple risk factors, to help see how factors interact and to look for confounding. The possibility that the apparent risk associated with work on a military base might be due solely to the drinking and smoking habits of military personnel was mentioned briefly in one of the papers cited⁶ and has been dealt with at greater length elsewhere.⁷ The possibility was investigated both by stratification and by multifactorial analysis. The conclusion was that work on a military base was an independent risk factor not associated with beer or cigarettes. Subsequently we have also taken severe diarrhoea into account in this model, and work on a military base remains a significant independent risk factor (relative risk 2.03). Hence we have to look for a different cause for this risk—possibly microwave radiation.

Rather than try to put all 11 risk factors^{1,6} into a model we first omitted two, spironolactone and nifedipine, both of which were marginal with small numbers and where spironolactone is a component of another risk factor—'steroids'. Logit analysis of the remaining nine shows the usual dependence on the order in which variables are entered into the model. Diabetes, myopia, and glaucoma emerge as the most powerful independent risk factors. Renal failure appears as a risk factor if entered before diabetes but not if entered after diabetes, which is consistent with our report that four of the seven renal failure patients in the study were insulin-taking diabetics. All four were cataract cases. The other risk factors, steroids, severe diarrhoea, 'heavy beer drinking', 'heavy smoking', and work on a military base, showed no particular confounding interactions and are marginal risk factors as originally reported.^{1,6,7}

Since the submission of our original paper in January 1987 we have completed a second case control study on 423 cataract patients and 608 controls aged 50 to 79 years (Harding, Egerton, and Harding, unpublished results). In this study we have confirmed diabetes, myopia when young, and glaucoma as major independent risk factors, with severe diarrhoea as a risk factor in septuagenarians. We have identified a new association with peripheral neuropathy. More importantly we have confirmed the protective

effect of aspirin-like analgesics; and have shown that low doses of aspirin, paracetamol, and ibuprofen are associated with the protective effect. In that study we have used log-linear and logit analysis to show that each of these three drugs is associated independently with the protective effect. Low doses of these drugs were associated with a halving of the risk of cataract.

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Perfluoropropane

SIR, We should like to report a case where the intraocular gas, perfluoropropane (C3F8), was used to reform a flat anterior chamber occurring after fistulising surgery. The technique may be of value to others facing this problem.

A 68-year-old man underwent routine trabeculectomy. From the first postoperative day the eye was hypotonous and the anterior chamber shallow. By the fourth day large choroidal effusions were present and cornea-lens contact had developed.

The anterior chamber was reformed with sodium hyaluronate (Healonid) and the sclerostomy sutured tightly shut. Unfortunately by the seventh day after trabeculectomy cornea-lens contact had recurred. The anterior chamber was again reformed with sodium hyaluronate and the choroidal effusions partly drained, but 72 hours later cornea-lens touch was present. On this occasion a bubble of 12% C3F8 was injected through an oblique track in the cornea into the anterior chamber without drainage of the choroidal effusion. This concentration is non-expansile¹ and was used in sufficient volume, approximately 0.5 ml measured in the syringe, to reform the anterior chamber.

The bubble filled the anterior chamber for five days before slowly being absorbed, so that 12 days after injection aqueous filled more than half the chamber. Nineteen days after injection aqueous completely filled the anterior

chamber, the choroidal effusions had disappeared, and intraocular pressure was normal. A single small anterior synechia persisted above.

Axial measurements of corneal thickness taken from the time of insertion of C3F8 showed a gradual thinning, from 0.75 mm to the 0.65 mm of the unoperated eye 12 days after injection. The anterior lens capsule has developed a localised opacity and reduplication of the capsule. This may be related to the episodes of cornea-lens touch or the C3F8.

Choroidal effusions after fistulising surgery are relatively common,² and as most resolve with time treatment can be expectant. When complicated by cornea-lens touch some procedure to reform the anterior chamber is justified. Our experience with this patient demonstrates some of the deficiencies of traditional methods of reformation. The injection of gas may be an approach which will allow sufficient time for the choroidal effusions to resolve.

Since preparing this report we have become aware of the case report by Wilson *et al.*,³ and their experience would seem to agree with ours.

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Treatment of a retinal embolus by photocoagulation

SIR, Occlusion of the retinal arterial tree by an embolus commonly results in permanent visual dysfunction despite early immediate treatment. This is in part due to failure in displacing the embolus. We report a case in which long-duration, low-intensity argon laser photocoagulation was successful in melting a presumed cholesterol embolus and restoring vascular perfusion of the retina.

Case report

A 52-year-old woman presented with a seven-hour history of sudden-onset, inferior, altitudinal visual field loss and blurring of vision in the right eye. Clinical examination revealed a visual acuity of 6/9, confirmed the visual field loss, and demonstrated an embolus at a bifurcation of the superior retinal arteriole. Ocular massage, rebreathing, and intravenous acetazolamide failed to dislodge the embolus. Argon laser photocoagulation was then applied directly to the embolus. Argon blue-green light was used with a 50 µm spot size set at 0.1 watt and continuous. During the laser

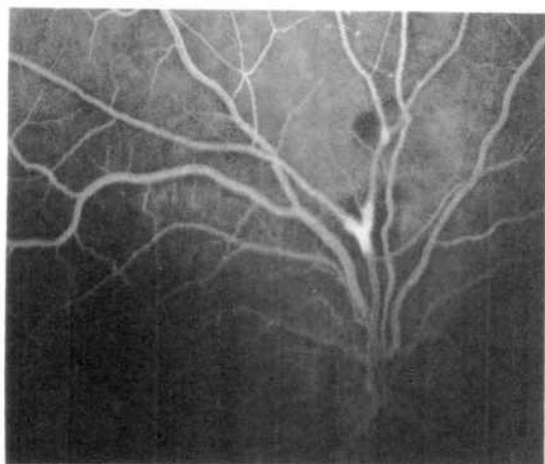


Fig. 1 Fluorescein angiogram in the late venous phase showing leakage of dye and surrounding choroidal hypofluorescence at the sites of photocoagulation.

application the embolus was noted initially to pulsate and then it melted, disappeared, and reappeared at the next bifurcation where treatment was reapplied, and the embolic material was seen to disappear into the peripheral retinal vascular tree. Unfortunately in this case there was no recovery of visual function. Fig. 1 shows the appearance of a fluorescein angiogram taken 24 hours after treatment. A further angiogram taken one week later demonstrated no vascular leak.

To our knowledge treatment of retinal emboli by long-duration, low-intensity argon laser photocoagulation has not hitherto been reported. Although in this case no visual function was restored, consideration could perhaps be given to this treatment in cases in which 'traditional' treatment has been unsuccessful.

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Needle holder with gap joints

SIR, Although very fine suturing usually requires suture tying forceps, there are many circumstances when time can be saved by the use of the needle holder, especially, for example, in tying sutures used for closure of conjunctival or skin wounds and in operations for squint and retinal detachments. Sometimes the suture material is entrapped in, or even cut by, the joints of the standard needle holder.

Fig. 1 shows the modification of the joints which avoids this entrapment. There is a generous gap between the shoulders, which are also rounded off to prevent snagging (which may occur even when entrapment has been avoided). Box joints have also been incorporated, partly to reduce the height of the shoulders on each side but mainly to improve

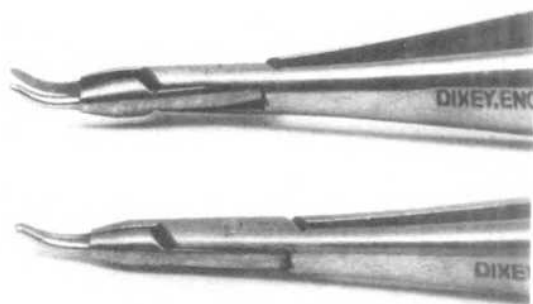


Fig. 1 Note the gap in the joints and round shoulders (upper) which prevent entrapment of sutures when the needle holder is used for suture tying. The box joints (lower) improve stability.

stability of the joints: box joints are not essential to the principle.

The basic needle holder we have chosen for this modification is the Barraquer pattern with curved jaws which has been such a fundamentally original contribution to ophthalmic and other surgery.¹⁻³ Other needle holders could be adapted in the same way. We have used this modified needle holder successfully in many operations, particularly for squint, eyelid surgery, and dacryocystorhinostomy.

The needle holder has been specially made by Dixey Instruments Ltd, 19 Wigmore Street, London W1A 4DU.

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Book reviews

Eye Movement Disorders. Eds. E A C M SANDERS, R J W DE KEIZER, AND D S ZEE. Pp. 280. £79.95. Kluwer: Dordrecht, Netherlands. 1987.

This book constitutes the proceedings of a symposium held in the Netherlands in 1986. There are sections on anatomy and physiology, clinical and paraclinical (whatever that is) examination, ophthalmic causes of diplopia, myogenic disorders, neurology, and treatment. The various contributors are either ophthalmologists, neurologists, neurosurgeons, orthoptists, or basic scientists.

Of the contributors only four out of 29 are not based in the Netherlands and about half are from Leiden University Hospital. The preface, written by Neil Miller, states that the symposium was 'aimed towards orthoptists, ophthalmologists, optometrists, neurologists and neurosurgeons'. Unfortunately in aiming for this broad spectrum of interest I think that the editors may have failed to make the book of adequate interest to the average ophthalmologist.

There is a great deal of duplication. The anatomy and applied physiology of eye movement control and the role of the parafloccular reticular formation are summarised no less than five times under various chapter headings. Evidently each speaker began his talk with a brief preamble and this was not removed or rationalised in the editing process. In general the anatomy and physiology section covers the matter under review well and is well illustrated and to the point.

In the section on clinical and paraclinical examination there is a useful section on recording eye movements, but there is remarkably little on tests for bilateral acquired IVth nerve palsy and nothing on tests for the presence of cyclotorsion or on serial measurement of the field of binocular single vision. There is nothing on the cocontraction syndromes such as Duane's syndrome and vertical retraction syndrome, which are among the more interesting abnormalities of eye movement.

The section on myogenic disorders is to my mind the best in the book. There are some good papers here on the histochemistry or extraocular muscles and on ocular myopathies and myasthenia. For some reason, however, there is an entire chapter on ptosis, which is good but hardly qualifies as an eye movement abnormality.

In the neurology section the chapter on nystagmus is good so far as it goes. There is little or nothing on congenital nystagmus or latent nystagmus and nothing on the possible causation of these conditions, though earlier on in the anatomy and physiology section the work of Hoffman is briefly alluded to. This work is highly relevant to the suggested pathogenesis of congenital and latent nystagmus, and it is surprising that there is no reference to it. There is a good chapter on disorders of gaze and some useful references on vestibular eye movement disorders. There is an excellent review of the literature on ocular motor disturbance and extraparamidal disorders, with a very useful bibliography. Sadly, in the section on psychogenic eye movements it is implied that blepharospasm is a psychogenic disorder, whereas most authorities would nowadays agree that it falls much more into the realm of dystonia and can no longer be classified with other psychiatric disorders and psychosomatic disorders.

In the chapter on treatment botulinum toxin is described as a somewhat experimental treatment in the management of diplopia. Although this symposium was prepared two years ago, it would still seem an inappropriate suggestion in view of the amount that has been written on this agent in the world literature to date.

The section on eye muscle surgery and peripheral IIIrd, IVth, and VIth nerve palsy by Marc Gobin is entirely adequate so far as it goes in that it describes Professor Gobin's own approach. He is also to be congratulated in being the only contributor in the entire eye movement disorder symposium to mention bilateral IVth nerve palsies as a possible problem presenting to the clinician, but for

some reason he fails to mention extorsion of the eyes and its effect on sensory symptoms. I also find myself concerned that in a chapter on eye muscle surgery and cranial nerve palsy there is no statement or even suggestion that adjustable suture techniques can be of value in these patients.

The final chapter is an article about neurosurgical aspects of tumour induced diplopia which mainly involves the treatment of the causation of eye movement disorders, but has nothing really in it about the actual disorders themselves. It seems to be an afterthought in a symposium which otherwise has not addressed neurosurgery directly.

In addition to the points raised about the lack of coverage of so-called musculofascial syndromes and of congenital nystagmus there is almost nothing in this symposium about concomitant squint. There is no mention of the congenital strabismus syndrome with dissociated vertical deviation and latent nystagmus, and there is certainly no attempt to address the possible causation of various types of strabismus.

The book has been somewhat sloppily edited. There are many minor spelling mistakes; the index is rather poor. On a number of occasions matters covered in the text are not indexed to the right page. The illustrations are in general of reasonable quality, though the black-and-white reproduction is occasionally difficult to interpret. There is one striking illustration, Fig. 3, paper 114, which claims to show an orbital varix both before and after a Valsalva manoeuvre on the same single still photograph.

The interested reader who wants a book for his own shelves on eye movement disorders would be better advised to purchase Leigh and Zee's *The neurology of eye movements*, which has excellently organised chapters and a first class bibliography. I think that this book should probably have a place in large ophthalmic libraries, as in particular the muscle section would be hard to reproduce elsewhere, but I feel it does not really address the matter of eye movement disorders for either the clinician who wishes to learn something about the area or the person who has already got an established interest in the field. JOHN P LEE

Baillière's Clinical Immunology and Allergy: International Practice and Research. Vol 1, No 1. **Endocrine and Other Organ-Oriented Autoimmune Disorders.** Eds. D DONIACH AND G F BOTTAZZO. Pp. 250. £19.50. Baillière Tindall: London. 1987.

Clinical immunology has seen a rapid expansion in the last decade and to non-specialists has become a complex subject. This book is an excellent summary of recent work on organ-specific autoimmunity in relation to the aetiology of a range of diseases. Some of them are admittedly quite rare, such as Carpenter's syndrome or Schmidt's syndrome, but the net also catches some important adult diseases, such as type I diabetes mellitus. The subject cuts right across the usual boundaries of clinical medicine, and there are excellent chapters dealing with thyroid disease, gut autoimmunity, and pituitary and hypothalamic disorders. As the editors point out, even though some of these diseases are rare, if the steps in their aetiology were thoroughly understood a more effective treatment might be developed for some of the other commoner disorders—provided the mechanisms have a common basis. The test of course will be to see if the knowledge produced by the studies reported in

this volume leads to a cure of, for example, type I diabetes mellitus. The processes are clearly complex, involving the interaction of genetic, virological, immunological, and environmental factors, so it seems difficult to pinpoint which are the key points to attack. The answers at present do not appear to be known, but the contributors to this volume demonstrate a large number of imaginative and fascinating studies in this field. For readers who want an overview of where work on organ-specific autoimmunity has reached I think this volume is to be highly recommended.

D J GALTON

A Colour Atlas of Ophthalmology. 2nd Edn. By A S M LIM AND I J CONSTABLE. Pp. 147, £10.95. Wright: Bristol. 1987.

This is the second edition in English of the colour atlas that was first published in 1979 with the aim of assisting in the teaching and practice of ophthalmology for general practitioners and other non-ophthalmologists, including nurses, medical students and paramedical staff. Both authors are internationally known, and have wide teaching experience.

The first edition was very well received and it was widely translated. The second edition more than maintains this high standard. The text is concise and well written; the illustrations are profuse and in colour and of excellent quality, though it is a little awkward to find them at the end of each chapter rather than with the text—it would probably be difficult to organise this otherwise. Both in its size and its price this book will be suitable for the pockets of those to whom it is directed. It should be highly successful.

M G FALCON

Community Ophthalmology. By SYED MODASSER ALI. Pp. 144. Tk.150. Anamoy: Bangladesh. 1985.

The significance of this small textbook is that it is the first one to appear on the emerging subject of community ophthalmology. As Professor M A Matin says in his introduction, it is 'by all standards a timely book.'

The first four chapters deal with the theoretical basis of community ophthalmology: What is a community? What is meant by community eye health? There is a good section on community diagnosis. The author puts the real cause of most blindness in the developing world where it belongs: poverty, ignorance, and lack of services in rural areas. There is a good section on community ophthalmology, emphasising the difference between conventional ophthalmic practice and the function of the ophthalmologist in his new role as a team leader. The sections dealing with primary health care and primary eye care are rather theoretical and idealistic. It is difficult actually to visualise what may be going on in a country such as Bangladesh. It would be a great benefit to the understanding of community ophthalmology if the author in future would give us the benefit of how this works out in practice in Bangladesh and some of the problems encountered and how they have been overcome.

The author has thought in detail about the function of

primary eye care workers—their role in examination of the eye and the types of treatment they may be able to undertake. By the standards of other countries these plans for the clinical activities of the primary eye care worker are somewhat ambitious, and again it would be useful to know how they work out in practice in Bangladesh.

Fifty-three pages deal with the major blinding diseases—xerophthalmia, trachoma, onchocerciasis, cataract, ocular trauma, and glaucoma. Under each heading the author discusses the aetiology, risk factors, epidemiology, and methods of intervention which are possible. There is then a detailed consideration of the action required at primary, secondary, and tertiary levels and the organisational aspects, including planning and evaluation.

The copy we were sent for review dates from 1985 and therefore inevitably some aspects are out of date. The number of blind by present WHO criteria is exaggerated. The drug ivermectin is not mentioned in the section on onchocerciasis, and the final outcome of the large number of people with temporary visual loss in the Bhopal disaster could not be included. There are many spelling mistakes.

These comments, however, do not detract from the author's achievement in being the first person to set down in one book the framework of community ophthalmology. Those involved in this emerging specialty will wish to have a copy in their library.

GORDON J JOHNSON

The book can be obtained from Anamoy Publishers, 367 Elephant Road, Dhaka-5, Bangladesh.

Near Visual Acuity Tests and Professional Vision Testing Charts. By MATTHIAS SACHSENWEGER. Pp. 62. £14.95. MTP: Lancaster, Lancs. 1987.

This book is a translation from the German and is a comprehensive collection of test types of all forms including standard printers' point types (N types) familiar to most British ophthalmologists, as well as texts in French and German and some in Gothic script, and Landolt's C and E and illiterate type diagrams. There are also specialised vocationally orientated test diagrams for microscopy and cytometer slide reading, Vernier reading, chemistry, mathematics, electronic diagrams, etc, and aerial photographs such as might be used in photogrammetry. In addition, there are unusual types such as might be displayed on video low vision aids and also samples of Moon and braille characters for those with no sight.

While the standard test types are well laid out, it is unlikely that the specialised types such as the Landolt's Cs would be of clinical value for use at 1 metre. Equally, the cytometer and microscopy plates, while demonstrating the work requirement, would be better replaced by actual slides in the cytology laboratory. The photogrammetry plates suffer from unavoidable printing problems such as variable and low contrast. The anaglyph stereo colour plate, while of interest, is not sufficiently well planned to include distractor information and would not be diagnostic. In summary, this book is likely to be a comprehensive work of reference for the varying types and vocational displays rather than a clinical test type aid.

C G F MUNTON

Management of Ocular, Orbital, and Adnexal Trauma. Eds THOMAS C SPOOR, FRANK A NESI. Pp. 445. US\$ 106.50. Raven Press: New York. 1987.

This book is edited by two ophthalmologists who have tried to emphasise the importance of a multidisciplinary approach to ocular, orbital, and adnexal trauma. It is a multi-author book with chapters by ophthalmologists, neuroradiologists, and facial plastic surgeons, but the overwhelming emphasis is on ophthalmology.

It is divided into three main sections. The first deals extensively with ocular trauma, and there are chapters on the primary care of the ruptured globe, anterior segment and corneal trauma, traumatic hyphaema, retinal and vitreal injuries, endophthalmitis, and antibiotic usage. Newer and sometimes controversial treatments are mentioned such as ascorbate and acetylcysteine therapy for chemical burns, cyanoacrylate for corneal defects, and aminocaproic acid for hyphaemas. The risks of sympathetic ophthalmitis are accurately given with references, and the special problems of preventing amblyopia in children are discussed. The second section is devoted to orbital trauma and covers the neuro-ophthalmological manifestations of trauma, radiology, maxillofacial and blow out fractures, orbital infections, and haemorrhages. The last section covers eyelid trauma with chapters on soft tissue injuries and scar revision, ocular adnexal damage including repair of lacerated canaliculi, and eyelid burns. There is a large section on eyelid reconstruction, and the inability of tarsorrhaphies to counteract tissue loss and protect the eye, especially after burns, is correctly stressed.

The difficulty with any book on trauma is to decide how extensively to explore specific topics. The requirements of different specialties vary, but this book achieves its aim of covering ocular, orbital, and adnexal trauma from the ophthalmologist's view point. It contains many interesting facts involving all specialties, such as that an operative consent form in the USA is not legal if the patient's alcohol level is over '100 mg/ml'. It is an excellent book for ophthalmologists in training or the general ophthalmologist who wants a current text on trauma management, but even for the experienced ophthalmologist its extensive references make it potentially very valuable with the increase in medicolegal work.

J R O'COLLIN

Notes

Colour Vision

The International Research Group for Colour Vision Deficiencies (IRGCVD) will hold its 11th symposium in Tokyo on 26–28 March 1990 in affiliation with the International Congress of Ophthalmology. The symposium will be at the Tokyo Medical College Hospital, 6–7–1 Nishi-Shinjuku, Shinjuku-ku, Tokyo 160, Japan.

Clinical trials booklet

A new edition of the booklet, *Clinical trials supported by the National Eye Institute: evaluating new approaches to the treatment of eye and vision disorders*, is now available. This publication gives brief information on 20 clinical trials currently supported by the NEI, including the purpose and design of each trial, patient eligibility criteria, patient recruitment goals, and a bibliography for completed trials. It also lists the names of professional and institutional participants, study chairmen, participating clinical centres, resource centres, and data and safety monitoring committee members. Copies obtainable from Ms Judith Stein, Information Officer, National Eye Institute, Building 31, Room 6A32, Bethesda, Maryland 20892, USA.

Albino Fellowship

In celebration of its tenth anniversary the Albino Fellowship will hold a scientific colloquium on the neurological and genetic aspects of albinism at Keble College, Oxford, on 27–30 September 1989. Details from Dr WOG Taylor, 16 Ronaldshaw Park, Ayr KA7 2TJ.

Rotary Club appeal

The Rotary Club of Delhi, India, has started a charitable eye hospital for the poorest members of the community. It has 12 beds and proposes increasing them to 24. An appeal for the donation of surplus instruments and equipment is being made by Mr B Sayal, LDS RCS, 1 Rosslyn Gardens, Wembley, Middlesex HA9 7NY (tel. 01-904 2736), who undertakes to collect them in the Greater London area.

Electrophysiology of vision

The 28th Symposium of the International Society for Clinical Electrophysiology of Vision will be held as a satellite symposium of the 26th International Congress of Ophthalmology on 10–14 March 1990 at Guangzhou, China. The deadline for abstracts is 1 November 1989. Details from Professor Lezheng Wu, MD, Zhongshan Ophthalmic Center, SUMS, 54 Xianlie Road, Guangzhou 510060, PR China.

All India Conference

The 48th All India Ophthalmological Conference will be held on 5–8 January 1990 at Ahmedabad, India. Details from the General Secretary, Dr J Agarwal, All India Ophthalmological Society, Dr Agarwal's Eye Institute, 13 Cathedral Road, Madras 600 086, India.

Glaucoma Convention

A glaucoma convention will be held on 14–15 July 1990 at Madras, India. Details from the Organising Secretary, Dr Chander Neroor, Glaucoma Convention, Dr Agarwal's Eye Institute, 13 Cathedral Road, Madras 600 086, India.

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Short Course in Tropical Ophthalmology: 29 January - 2 February 1990

A five-day course in Tropical Ophthalmology will be held at the Institute of Ophthalmology, Cayton Street, London EC1, from 29 January to 2 February 1990.

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Reference 1. Leibowitz HM, Berrospi AR, Kupferman A. Am J of Ophthalmology 1977; 83(3): 402-406.



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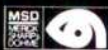
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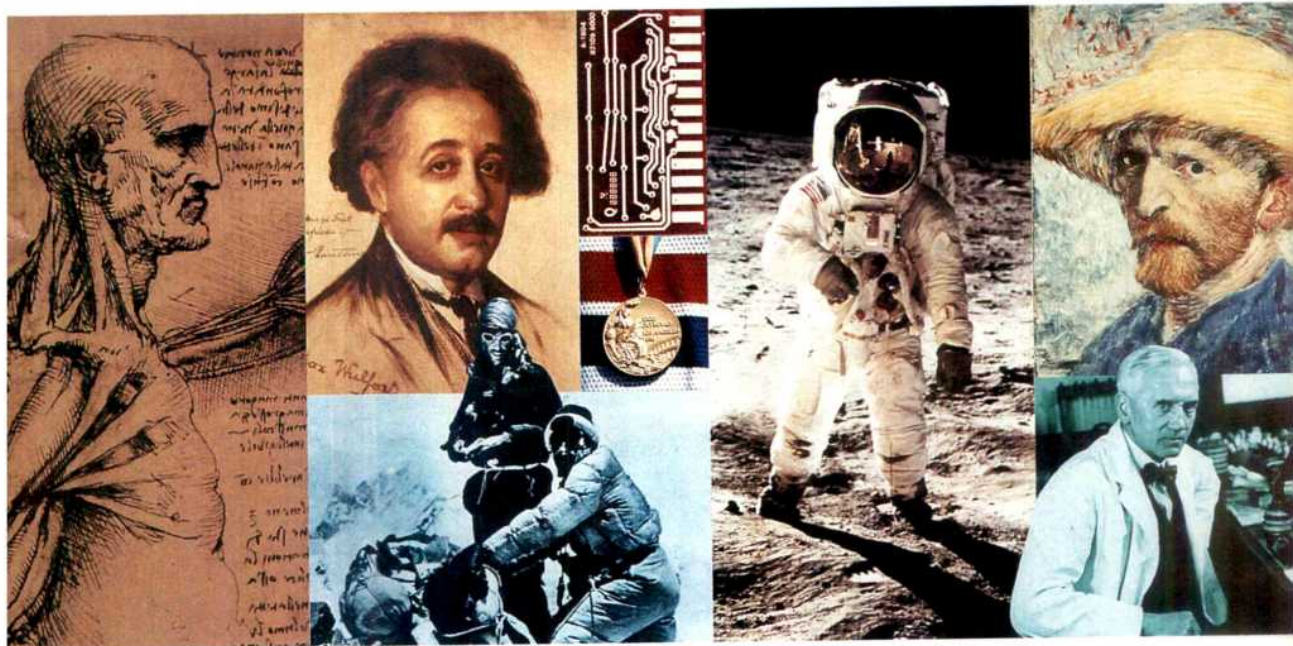
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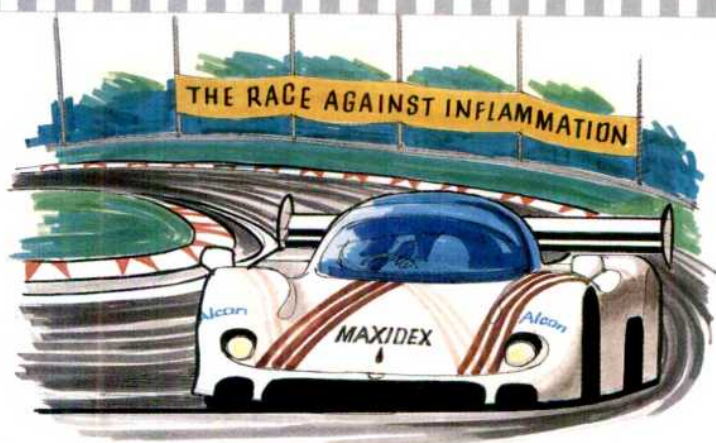
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Editorial: Expression of HLA antigens in the cornea

The paper by El-Ashar and colleagues this month (p 587) is unlikely to attract more than a passing glance from most clinicians, yet it centres on a subject that already has considerable clinical relevance, and it sets the scene for an examination of recent developments in corneal immunology, particularly transplantation. Its main conclusion is that class II human leucocyte antigens (HLAs) can be expressed on the corneal epithelium and endothelium, and we need to examine why this is important, beginning with a summary of the role of class I and class II antigens.

Class I antigens, encoded by three main regions (HLA A, B, and C), are glycoproteins that are formed on the surface of all nucleated cells. Their natural function is that they are required for the successful interaction of T lymphocytes of the killer subset (CD8+) with self cells which have foreign antigen (particularly viral antigens) on their surface: the CD8+ cells react with self plus antigen ('dual recognition') to produce cell lysis. Foreign (donor) class I antigens in a transplant can be treated in a similar way, specific CD8+ cells seeing them as 'self plus x', with consequent damage to the graft. A good deal of painstaking work has shown that some degree of compatibility between donor and host class I antigens (tissue matching) does, as expected, slightly reduce the incidence of corneal graft rejection in high-risk patients, but there are so many class I antigens that a really good match is highly improbable. Low-risk patients have such a good prognosis that the expensive and time consuming process of matching is not justified for the doubtful benefits.

Class II HLA antigens (encoded by the D region) are also glycoproteins, but they are normally more restricted to cells concerned directly with immune responses, such as B cells and macrophages and the antigen presenting cells in the corneal epithelium (Langerhans cells) and stroma (interstitial dendritic cells). Their natural function, again by 'dual recognition', is to guide helper T (CD4+) cells in their interaction with antigen presenting cells, and with B cells, so that this interaction is normally (and quite appropriately) restricted to them. It would usually be unsatisfactory if other cells triggered these reactions. However, it has been realised recently that this can sometimes occur. Liver cells for example can express class II antigens under the influence of interferon during inflammation, and

we now learn from El-Ashar and colleagues that corneal epithelial and endothelial cells can do just the same. This has a particularly important bearing on transplantation, as well as taking us further towards unravelling the pathogenesis of some types of corneal inflammatory disease.

In the unnatural milieu of transplantation it appears that donor class II antigens, borne on the antigen-presenting cells in the corneal disc, are the main stimulus to the afferent limb of the allograft reaction: they induce CD4+ cells to promote the differentiation of CD8+ cells (via lymphokines such as interleukin 2) which may then destroy the graft. Host antigen presenting cells may be able to initiate the afferent limb by processing donor class I antigens, but this is a much weaker stimulus. It does indeed appear that class II (HLA D) antigen matching reduces the incidence of rejection, and so may attempts at reducing the class II antigenic load in the donor. Various experimental methods, and the procedure of organ culture for donor corneal storage, reduce the Langerhans cell count and probably reduce the incidence of rejection. But, surprisingly, a carefully conducted prospective trial by Stulting and colleagues¹ (published since the paper by El-Ashar and colleagues was submitted) showed that removal of the donor epithelium (and hence the Langerhans cells) did not. Perhaps too many class II bearing cells remain in the stroma.

It is all the more worrying to learn now that class II antigens could be expressed both by the corneal epithelial and endothelial cells in states of inflammation. Either this could lead to rejection *de novo*, if the inflammation was not caused by it in the first place—and this could be one further explanation for the observation that rejection so often seems to follow inflammatory disease such as herpes. Or it could lead to a spiral of worsening rejection if rejection was the original cause of the inflammation.

How fortunate we are in ophthalmology that topical steroids are usually so effective at all stages of the rejection process. But perhaps we should be even readier to use them preventively—particularly before, as well as after, the graft.

M G FALCON

Reference

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Editorial: Melanoma of the iris

The paper by McGalliard and Johnston in this month's issue (p 591) prompted me to read some of the literature on ocular melanomata. 'Iris tumours rarely metastasise, and the mortality is much less than in similar tumors of the ciliary body or choroid. They are easily seen and ordinarily are removed at an early stage.'¹

This statement was published in 1962, long before McLean and colleagues' bombshell suggesting that enucleation increased the chances of metastasis from malignant choroidal melanoma.² The trouble is that the first statement is at variance with the second. If it is indeed true that metastasis from iris melanoma is less than from choroidal, the obvious assumption is that the lower frequency must be due to earlier diagnosis and hence earlier treatment. There is evidence that the chances of metastasis depend mainly on size³ and histological type.⁴ Therefore, if we assume that melanomata of the iris behave in the same way as those of the choroid, it does seem reasonable to assume that removing the melanoma when it is small would give the patient a better chance of survival than leaving it until it was larger. And, in accordance with this line of argument, one can easily see that the patient with an iris melanoma is more likely to survive, since for one thing it is almost impossible to allow such a lesion to develop to anything like the size of the average 'mushroom' choroidal melanoma, which by the time it reached its usual size would be capable of filling the anterior chamber three times over. Hence early removal of iris melanomata is more or less automatic.

The trouble is that if McLean and colleagues are right and enucleation of the eye predisposes to metastasis, one would have thought that excision of an iris melanoma ought to predispose to metastasis

as well, but clinical experience, quite apart from any published reports, clearly indicates that it does not.

As an ordinary ophthalmologist without pretension to particular expertise in oncology I certainly do not wish to get embroiled in controversy over enucleation versus radiation or observation, since, as readers of this journal will be aware, such matters can be debated with much energy with the resultant friction engendering some heat.⁵⁻⁸ I write merely as an ophthalmological 'man in the street' trying to make up my mind on such matters, according to what I read in the papers, in this case the ophthalmological papers. And I have to admit that so far I have not had it explained to me to my satisfaction why it should be a bad thing to enucleate for melanoma of the choroid but a good thing to excise a melanoma of the iris, at any rate so far as the long term survival of the patient is concerned.

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Recombinant interferon-gamma induces HLA-DR expression on human corneal epithelial and endothelial cells in vitro: a preliminary report

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SUMMARY The effect of interferon-gamma on the expression in situ of major histocompatibility complex (MHC) products in human corneas was studied in vitro. Incubation for four days with 5 or 50 mg/l of *Escherichia coli*-derived recombinant human interferon-gamma resulted in the appearance de novo of MHC class II or HLA-DR antigens on variable numbers of corneal epithelial cells as well as on corneal endothelium, whereas it had no effect on the expression of MHC class I or HLA-ABC antigens. These results may help to explain the mechanism underlying the expression of HLA-DR antigens on corneal and limbal epithelium in various inflammatory eye diseases.

Major histocompatibility complex (MHC) class II products or HLA-DR antigens are highly polymorphic cell surface glycoproteins involved in antigen presentation and initiation of T lymphocyte-dependent immune responses. HLA-DR antigens are predominantly expressed on immunocompetent cells such as B lymphocytes, activated T lymphocytes, macrophages, dendritic cells, and endothelial cells.¹ In addition a variety of epithelial cell types are now known to express HLA-DR antigens constitutionally or following induction with lymphokines.²

In the normal human cornea HLA-DR antigens are expressed on occasional dendritic cells in the epithelium and stroma^{3,4} and on the endothelial cells lining the limbal blood vessels.^{5,7} Normal corneal epithelium and endothelium, as well as the majority of stromal cells, lack HLA-DR antigens.

We recently observed HLA-DR antigen expression on corneal epithelium in herpetic keratitis,⁸ on limbal epithelium in phlyctenular eye disease,⁹ and on conjunctival epithelium in trachomatous conjunc-

tivitis.¹⁰ In all these conditions variable numbers of T cells were found in the epithelial and stromal inflammatory infiltrate, suggesting that lymphokines liberated by these T cells were responsible for the epithelial HLA-DR expression. The lymphokine, interferon-gamma, produced by activated T cells has been shown to induce synthesis and expression of HLA-DR antigens in a variety of epithelial cells in vitro.^{2,11}

In the present study we have investigated whether interferon-gamma can induce HLA-DR expression by the corneal and limbal epithelium in vitro.

Materials and methods

Eyes were obtained at necropsy within a few hours of death. The corneas used in this study were excised with a 3 mm scleral margin and divided into three parts. Each piece of cornea was placed in a separate bottle containing 10 ml of organ culture medium.¹² The first corneal part served as a control. To the culture medium of the second and third bottles human pure recombinant *Escherichia coli*-derived interferon-gamma was added in a dose of 5 and 50

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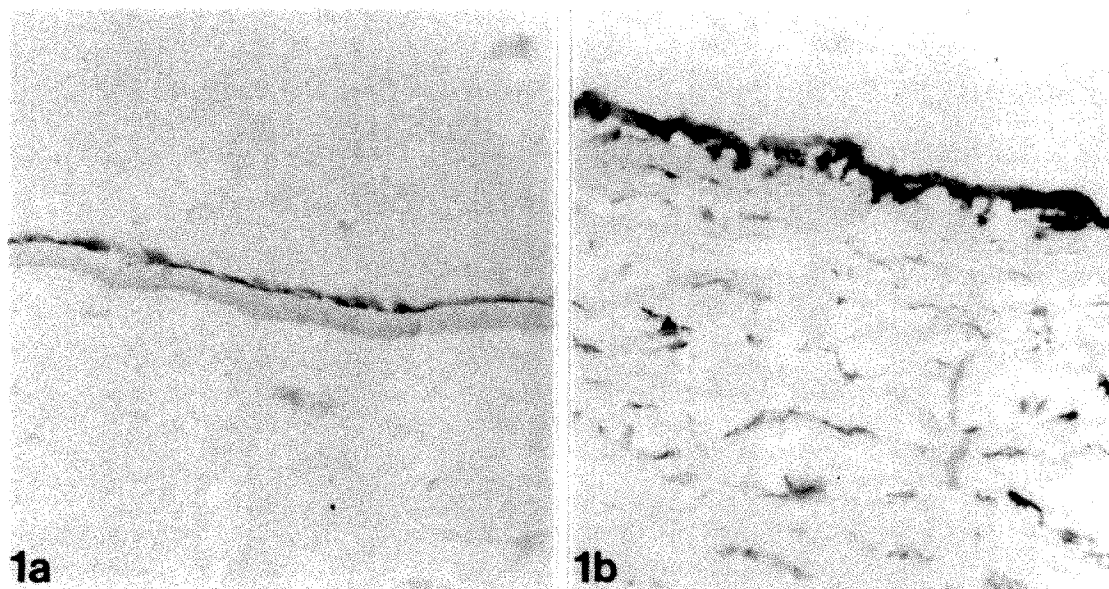


Fig. 1 Effect of interferon-gamma on HLA-DR expression by corneal endothelium. 1a. No endothelial reactivity is seen in the control specimen. 1b. Four days of incubation with 50 mg/l interferon-gamma reveals HLA-DR expression by corneal endothelium and by variable numbers of stromal cells.

mg/l respectively. Recombinant interferon-gamma was kindly supplied by Dr W Wolf (Bioferon GmbH & Co, Laupheim, West Germany). The three bottles

were incubated at 37°C in 5% CO₂ for four days; subsequently the corneal pieces were snap frozen in isopentane cooled liquid nitrogen.

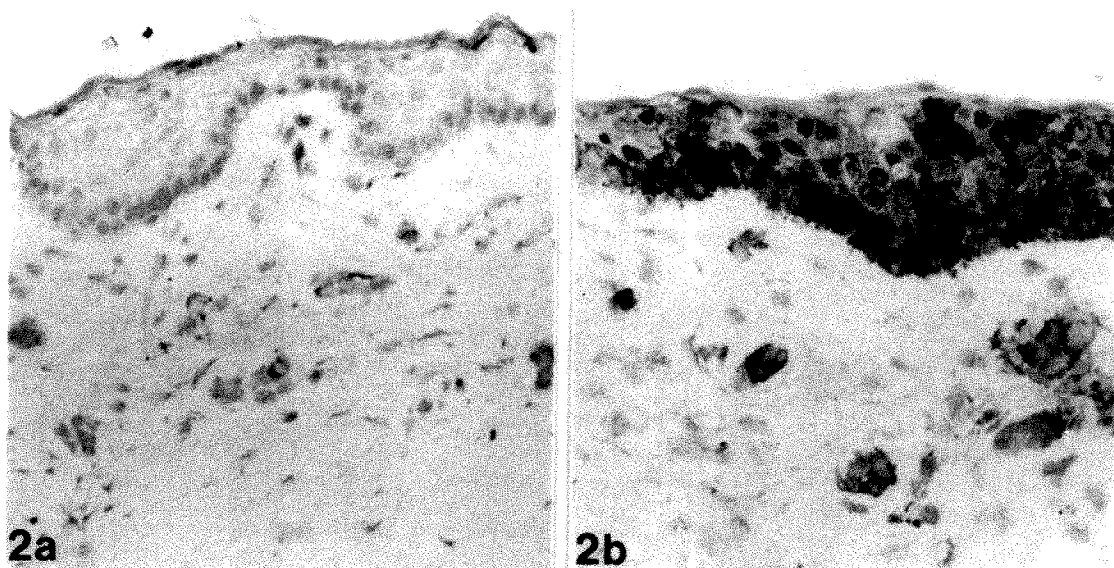


Fig. 2 Effect of interferon-gamma on HLA-DR expression by limbal epithelium. 2a. Weak reactivity is seen on the endothelium of some limbal blood vessels in the control specimen. 2b. Four days of incubation with 5 mg/l interferon-gamma reveals strong membranous and cytoplasmic HLA-DR expression by many epithelial cells as well as by the endothelium of most limbal blood vessels. (Three-step indirect immunoperoxidase method for TAL1B5, slightly counterstained with Harris's haematoxylin; all figures $\times 260$.)

Serial 5 μ m thick cryostat sections were stained with the three-step indirect immunoperoxidase method using monoclonal antibodies directed to MHC products. Monoclonal anti-HLA-ABC (Cappel Laboratories, Cochranville, PA) reacts with the constant part of HLA-ABC antigens. Monoclonal antibody TAL-1B5 was a generous gift from Dr W F Bodmer, Imperial Cancer Research Fund, London, and is directed against the monomorphic part of HLA-DR alpha chains,¹³ and monoclonal antibody L243 (Becton-Dickinson, Sunnyvale, CA), is directed against the monomorphic part of HLA-DR β chains.¹⁴

Results

The control cornea that did not receive interferon-gamma expressed HLA-ABC antigens on epithelial cells, stromal cells, corneal endothelium, and on the endothelial cells lining the limbal blood vessels. HLA-DR expression, identified with monoclonal antibodies L243 and TAL-1B5, was restricted to occasional dendritic cells in the limbal epithelium and corneal stroma as well as to the endothelium of limbal blood vessels (Figs. 1a and 2A).

After four days of incubation with interferon-gamma the expression of HLA-ABC antigens was similar to that of the control cornea. However, monoclonal antibodies L243 and TAL-1B5 showed additional membranous and cytoplasmic HLA-DR expression by the corneal endothelium (Fig. 1b) as well as by variable numbers of epithelial cells, the most intense reactivity being found in the deepest epithelial layers (Fig. 2b). This additional HLA-DR expression was found with both concentrations of interferon-gamma employed.

Discussion

In this study we have shown that MHC class I products or HLA-ABC antigens are expressed on normal human corneal epithelium and stromal cells. These data are in accordance with earlier findings⁵⁻⁷ and indicate that epithelial and stromal cells can serve as target cells involved in allograft rejection.¹⁵ Moreover, the high density of HLA-ABC antigens on corneal epithelium provides an explanation for the decreased rejection rates when the epithelium is removed prior to transplantation,¹⁶ as well as for the prolonged graft survival, observed in MHC class I matched corneal transplants.¹⁷

Normal corneal endothelial cells have previously been found to lack MHC class I products. Our demonstration of HLA-ABC antigens on corneal endothelium can be explained by the short term culture of the tissue fragments, a procedure that has

been shown in other studies to induce MHC class I products on corneal endothelium.¹⁸⁻²⁰

We have also shown that MHC class II products or HLA-DR antigens are normally present on occasional dendritic cells in the limbal epithelium and on endothelial cells lining limbal blood vessels. After incubation with interferon-gamma, however, corneal epithelial and stromal cells were found to express HLA-DR antigens. This finding in vitro confirms and extends previous studies on cultured rabbit²¹ and human epithelial and stromal cells.²²⁻²⁴ Moreover, the effect of low concentrations of interferon-gamma, namely, 5 mg/l, provides good evidence that epithelial HLA-DR expression in various inflammatory conditions in vivo is indeed induced by interferon-gamma, released by activated T cells.

Interferon-gamma also induced expression of HLA-DR antigens on corneal endothelium. This finding confirms previous studies employing cultured endothelial cells, and may indicate a potentiating role in the rejection of corneal allografts.¹⁵

HLA-DR expression by corneal epithelial and endothelial cells may render these cells susceptible to immunological attack by MHC class II restricted cytotoxic T-cells²⁵ or may render them capable of acting as antigen presenting cells for T cells, thereby enhancing the immune response and possibly inducing an autoimmune response.²⁶ Elucidation of the precise functional significance of corneal HLA-DR expression awaits further in-vitro studies.

This work was supported in part by the programme of scientific and clinical co-operation in the field of ophthalmic medicine and surgery between the University of Mansoura, Arab Republic of Egypt, and the Catholic University of Leuven, Leuven, Belgium.

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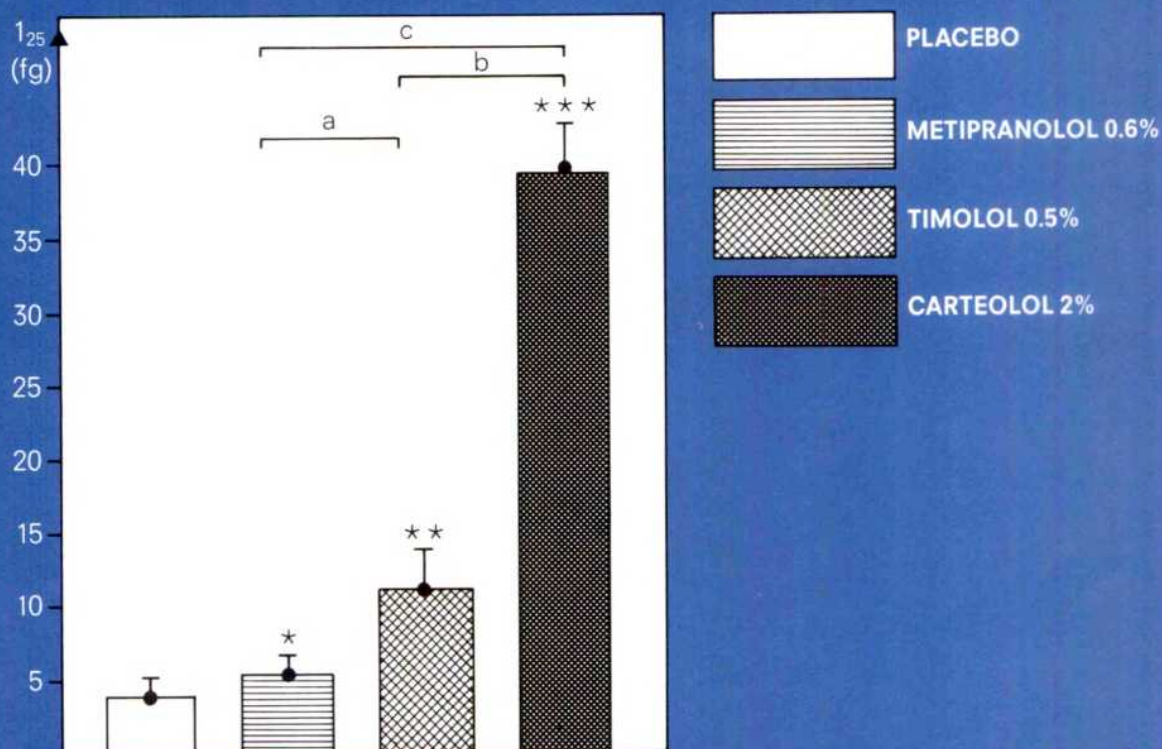
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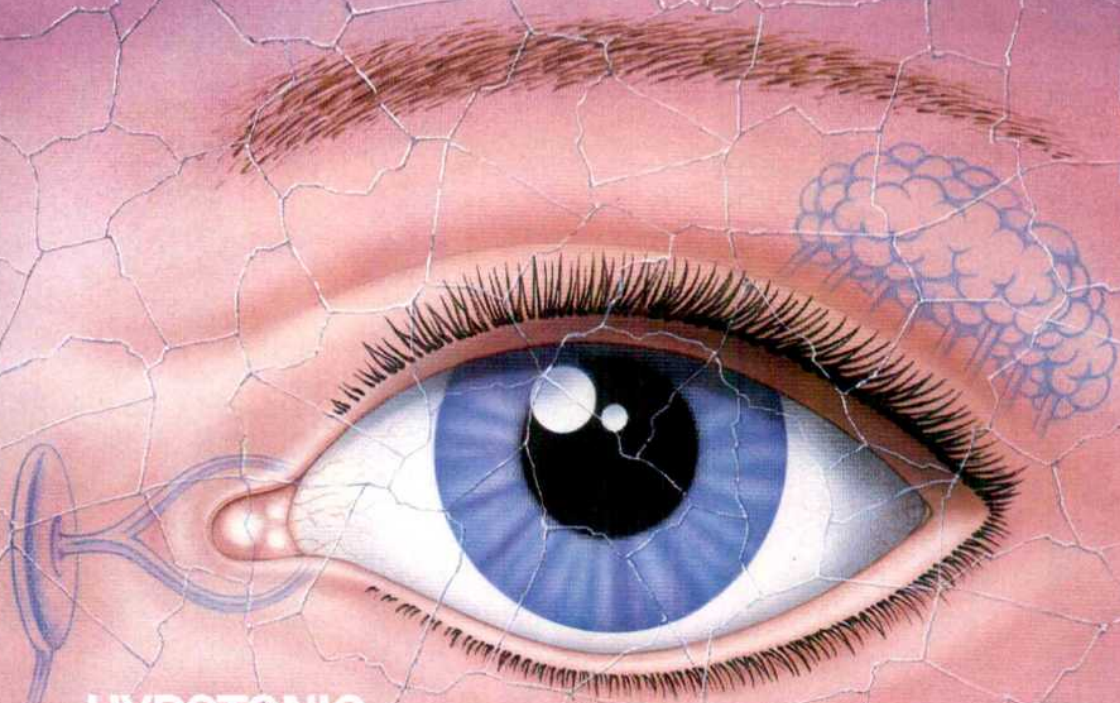
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A study of iris melanoma in Northern Ireland

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SUMMARY A retrospective study of all cases of iris melanoma in Northern Ireland over a 15-year period was undertaken. A total of 18 cases were identified. Of these, nine were histologically proved to be iris melanomas of various types. Within the period of follow-up two patients died from metastatic deposits. In both cases invasion of the anterior face of the ciliary body was present on histological examination. The implications for management are discussed.

Malignant melanomas of the uveal tract continue to pose considerable problems in treatment. Melanoma of the iris accounts for 3-10%^{1,2} of all uveal melanomas, and the indication for the surgical treatment of this tumour can be difficult in view of the reported low risk of metastatic spread. Nevertheless there have been well documented instances of death due to metastatic disease from iris melanoma.^{3,4}

We report our experience with all cases of iris melanomas seen in our department over the past 15 years.

Materials and methods

The records of all patients with iris melanoma were retrieved through medical indexing, theatre records, and fluorescein angiography records of the Royal Victoria Hospital, Belfast, for 1973-87. Since our hospital is the regional centre for Northern Ireland it can be taken that the incidence recorded in our study represents the prevalence in the population served (1.4×10^6).

Results

In our series nine patients had histologically proved iris melanomas, and nine other iris lesions were clinically diagnosed as being melanomas but were not subjected to biopsy or excision. The average age of the patients treated surgically was 57 years (range 43-79). The average age of those who were conservatively managed was 66 years (range 51-74).

Table 1 shows the patients who were managed by observation alone. Of these nine patients four gave a history of a melanotic lesion on the iris since child-

Table 1 Patients managed by observation alone

Patient, age, sex	Eye	Location	Follow-up (yr)	Growth	IFA
A, 73, M	R	Inferior	11	-	
B, 74, M	R	Inferotemporal	4	-	
C, 55, M	L	Inferotemporal	12	-	Vessels
D, 74, M	R	Inferonasal	2	-	Vessels
E, 62, M	L	Inferior	6	-	
F, 51, M	R	Inferotemporal	6	+	Vessels
G, 74, F	R	Superonasal	5	-	Vessels
H, 61, F	L	Inferotemporal	5	-	ND
J, 68, M	L	Temporal	9	-	

IFA=iris fluorescein angiogram. ND=not done.

hood. In the other five a lesion was noted on routine examination by an optician, general practitioner, or ophthalmologist. As can be seen from Table 1, each had a single lesion which did not involve more than one quadrant of the iris. Fig. 1 shows the appearance of case C. The two clinical photographs were taken five years apart and confirm the static nature of the lesion despite a well defined tumour circulation which was confirmed on fluorescein angiography. None showed a rise in intraocular pressure. Evidence of progressive enlargement of the tumour was shown in one case. None have shown extrascleral or metastatic spread.

Of the histologically proved cases three out of nine (33%) presented with secondary glaucoma and mild corneal oedema, three others presented with a progressive increase in size of the lesion, and two others were noted on routine eye examination. One patient presented with a spontaneous hyphaema. Four patients were treated surgically shortly after initial presentation with a variety of clinical features.

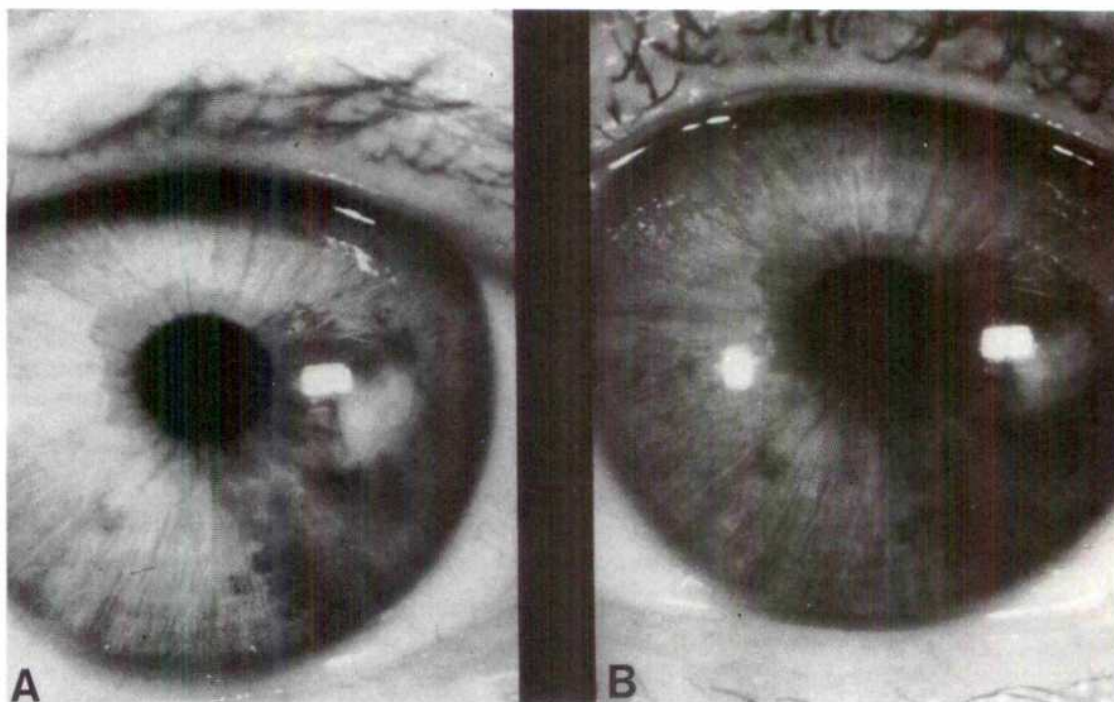


Fig. 1 Quadrantic sized melanoma with amelanotic centre. Photographs taken five years apart showing no change in size. A: March 1978. B: October 1983.

One had evidence of extrascleral spread, two eyes had loss of central vision due to disc cupping, and one patient had presented with a hyphaema. In the remaining five patients the lesions were recorded as growing slowly over the period of observation (range 1–5 years). Fig. 2 shows the clinical growth of the lesion in case 5 over a period of 18 months.

Tables 2 and 3 show the characteristics of the nine cases of histologically proved iris melanoma. Two tumours (22%) were found to be spindle A cell type, six (67%) were spindle B type, and one (11%) was a mixed spindle/epithelioid type. Both spindle A melanomas were treated by iridectomy and the patients were alive 10 and 14 years afterwards. Of the six patients with spindle B melanomas three were treated by enucleation and three by iridectomy. The patient with mixed type melanoma was initially treated by iridectomy, but after local recurrence enucleation was performed 14 months later.

Two patients (22%) died four and five years after enucleation as a result of metastatic spread of melanoma. Case 1 (mixed type) presented with a distortion of the pupil and a subjective awareness of change in the eye. A local excision was performed. At operation the anterior face of the ciliary body was seen to be invaded. Excision was thought to be incomplete on histological examination. The opera-

tion was complicated by lens extraction. Corrected aphakic vision was 6/6. Fourteen months later the residual tumour was increasing in size and enucleation was undertaken. Histology revealed extrascleral extension beneath the conjunctiva in the region of the limbus. Four years after enucleation the patient died from hepatic secondaries.

Case 3 (spindle B cell type) presented with extensive iris invasion and secondary glaucoma. The optic disc was cupped, suggesting a long-standing lesion. There was no clinical evidence of extrascleral spread. Enucleation was undertaken as a primary procedure. The histological report noted gross infiltration of the trabeculum and some extension posteriorly into the anterior face of the ciliary body but no extrascleral spread. Metastatic liver disease was noted at laparotomy five years later and death occurred within nine months.

Of the nine surgical cases four had fluorescein angiography of the anterior segments. All showed obscuration of the normal iris radial vessels and had a distinct tumour circulation within the lesion. Three lesions showed early leakage of the dye, and one lesion showed only late leakage. Of the observed cases eight had anterior segment angiography. Tumour circulation was seen in four of these, with early leakage evident. The remainder showed a

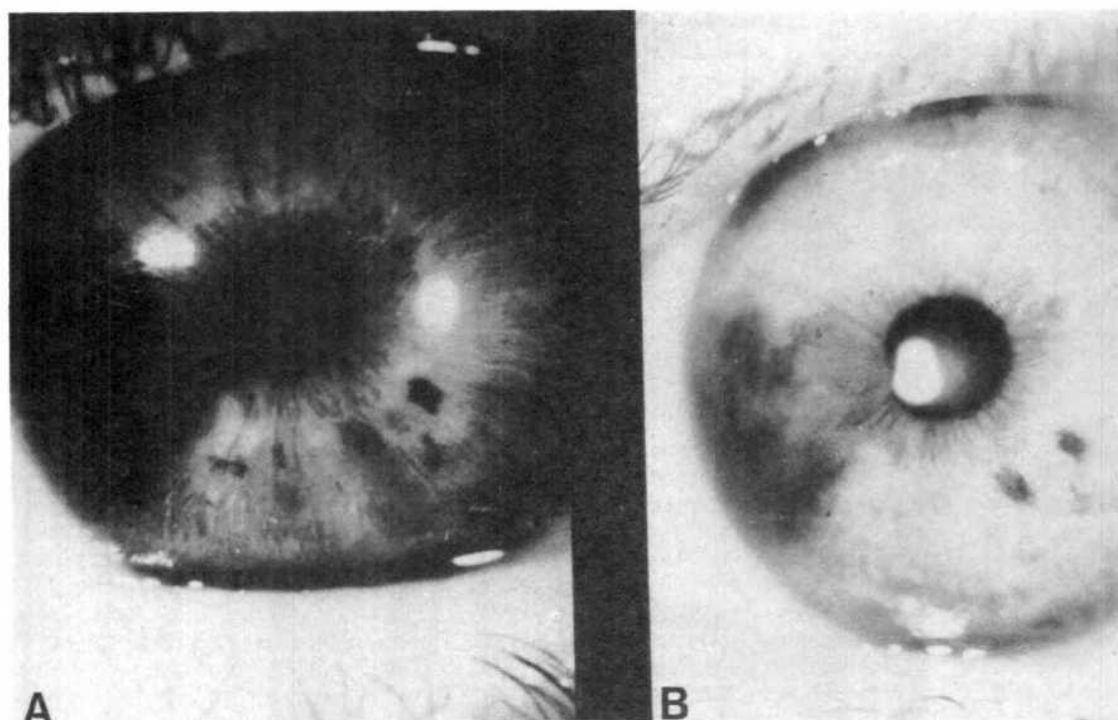


Fig. 2 Nasally located melanoma showing evidence of growth. Photographs taken 18 months apart. A: August 1984. B: February 1986.

variable degree of late leakage from the margins of the lesion (Table 1).

Discussion

In a study⁵ of choroidal melanoma enucleated in Northern Ireland over a 15-year period (1965–80) 100 cases were reported. In our study over a similar period (1973–87) nine histologically proved iris melanomas were treated surgically. Thus iris melanomas constitute approximately 9% of uveal melanomas. This correlates well with the findings of

other studies.^{1,2} As is well recognised, iris melanoma has a predilection for the inferior iris. This was confirmed in our series, only one of the tumours being located in the upper half of the iris. The reason for this tendency is unknown, but it is possible that the upper lid protects the superior iris from actinic exposure throughout life, thereby reducing the likelihood of melanocytic proliferation. Shields⁶ states that superiorly placed lesions are sufficiently rare for them to be considered as pseudomelanomas or as an anterior extension from a ciliary body melanoma. In our case G the melanotic lesion was evenly pigmented and slightly elevated, with some ectropion uveae. Only the inner half of the iris stroma was involved, with no extension into the angle or posteriorly. The appearances were therefore in keeping with a primary melanoma.

The average age at diagnosis of all patients with iris melanoma in our study was 61.5 years. This is considerably older (15–20 years) than in other published studies.⁶ Even the histologically proved cases had an average age of 57 years. Two of these gave a history of a melanotic lesion on the iris since adolescence or earlier. There were, however, no cases in our study of patients presenting in adolescence or early adulthood.

Table 2 Patients managed by surgery

Patient, age, sex	Eye	Location	Presentation	IFA
1, 62, F	L	Nasal	↑ size	ND
2, 49, M	L	Inferonasal and satellites	↑ IOP	Vessels
3, 47, F	L	Inferotemporal	↑ IOP	ND
4, 79, M	L	Ring	↑ IOP	ND
5, 43, M	L	Nasal	↑ size	Vessels
6, 51, F	R	Inferior	Routine	ND
7, 55, F	L	Inferonasal	↑ size	Vessels
8, 72, M	R	Nasal	Routine	Vessels
9, 59, F	L	Inferior	Hyphaema	ND

IFA = iris fluorescein angiography, ND = not done. ↑ = increasing.

Table 3 Patients managed by surgery

Patient	Treatment	Pathology	Features	Follow-up
1	Iridocyclectomy enucleation	Mixed cell	Invasion of ant. face of ciliary body and extrascleral spread	Died 4 years after enucleation, liver metastases
2	Enucleation	Spindle B	Extrascleral spread	Six months, well
3	Enucleation	Spindle B	Invasion of ant. face of ciliary body, no extrascleral spread	Died 5 years 9 months after surgery, liver metastases
4	Enucleation	Spindle B	Confined to iris, no extrascleral spread	Three years, well
5	Iridectomy	Spindle B	Complete removal	Two years, well
6	Iridectomy	Spindle A	Complete removal	Ten years, well
7	Iridocyclectomy cataract extraction	Spindle B	Complete removal	Two years, well
8	Iridectomy	Spindle B	Complete removal	One year, well
9	Iridectomy	Spindle A	Complete removal	Fourteen years, well

In recent years some authors have recommended a more conservative approach in the management of iris melanoma. Shield's indications⁶ for enucleation are those melanomas involving more than 50% of the iris with involvement of the angle and/or secondary glaucoma. He holds that patients with less extensive tumours showing evidence of growth can be successfully managed by local excision and states that in his experience over 50 patients have been managed thus without evidence of a tumour related death. However, tumour related deaths do occur with iris melanoma. The study by Sunba *et al.*³ reported seven cases of death from a primary malignant melanoma of the iris. Some of these cases had been treated by iridectomy with apparent complete removal of the tumour. An extreme example of the importance of follow-up is reported by Kersten *et al.*,⁷ who recorded a tumour related death 30 years after enucleation. Geisse and Robertson⁴ reviewed the English language literature on iris melanoma and reported a 3% overall incidence of metastases. Mixed type and epithelioid cell tumours had a metastatic rate of 10.5% and 6.9% respectively. Their own series of seven patients, with minimum follow-up of 10 years, had no deaths from metastases. Four of their tumours were spindle A forms, and it is generally held that metastases do not occur with these melanomas. The clinical problem lies in deciding which lesions are spindle A and which of these will progress to spindle B and epithelioid cytology. Several authors have argued that, since overall mortality rates are so low, all lesions should be observed. Their evidence is based on good long-term survival following local excision. Prolonged survival following excision cannot be equated with low risk in the absence of treatment.

In their series Jakobeic and Silbert⁸ described a nine-part classification of melanocytic lesion. Of their 189 cases 87% were thought to be benign in cytology and 13% were assigned to three malignant groups. Invasion of neighbouring structures such as

the trabeculum, causing glaucoma, or the ciliary body was not necessarily taken as evidence of malignancy. These were described as 'progressive naevi', and the lack of any tumour-related deaths was taken as evidence of their inherently benign nature.

Seven of our tumours corresponded to the three malignant groupings in Jakobeic and Silbert's classification. These groupings correspond to spindle B, mixed type, and epithelioid melanoma in other series. Two of our patients have already developed metastatic disease from their tumours and have died four years and five years nine months after enucleation. Both of these cases showed invasion of the anterior face of the ciliary body and one presented with secondary glaucoma. A clinical assessment of invasion of the anterior ciliary body is difficult, and if this is an important prognostic indicator then earlier local excision is indicated. Local excision, however, is not without problems. Since most of these lesions occur in the inferior iris, an iridectomy can often result in significant glare, and both our patients

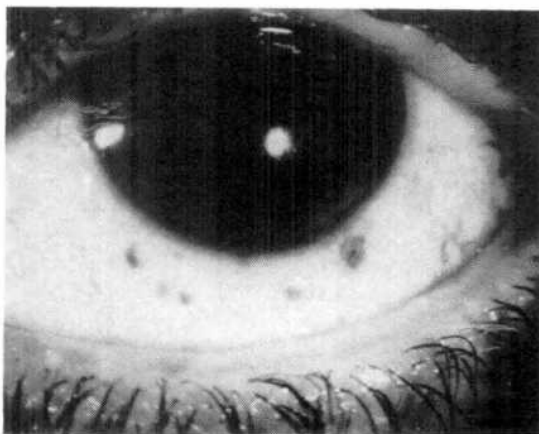


Fig. 3 Large melanoma involving the inferior half of the iris with extrascleral spread evident around the aqueous veins.

treated by iridocyclectomy required lens extraction.

Extrasceral extension indicating escape from the confines of the scleral envelope and access to the circulation is widely regarded as a bad prognostic sign in choroidal malignant melanoma.⁹ Sunba *et al.*¹⁰ identified this as a risk factor for iris melanoma. One of the cases of metastases and one other of our cases (no. 2) (Fig. 3) were noted to have this on presentation. Follow-up in the latter case has been limited so far, but the prognosis must be guarded. Early identification of those tumours which will progress to invade the ciliary body or pass through the sclera would be of great benefit.

The use of fluorescein angiography has been investigated in the hope that the angiographic features could be correlated with histological type. Demeler¹¹ classified the angiographic patterns into three groups and found a correlation between intrinsic vessels with early leakage of dye and a malignant cytology. Conversely the absence of vessels or leakage was shown to be associated with a benign histology. Other authors⁴ have confirmed this general rule but advise that fluorescein angiography should not be used as the final arbiter in the differentiation between benign and malignant lesions. Our results would confirm this, since four of the observed cases in our series showed a definite tumour circulation with early leakage, yet only one showed evidence of clinical growth over an extended period. Fluorescein angiography therefore is a useful ancillary tool in the management of malignant melanoma of the iris.

The criteria applied for observation of iris melanomas in this series have been: (a) no significant growth of the lesion; (b) no evidence of satellite growths; and (c) no evidence of progressive invasion of the trabeculum.

One patient, F, did not comply with these criteria because of refusal of excisional iridocyclectomy. This lesion progressively enlarged, with encroachment on the trabeculum, but the patient was adamant that no surgery be undertaken. Since then he has refused further follow-up but is known to be alive and well at present. All other cases have shown no significant

change in the lesion since presentation. Definite conclusions cannot be drawn from those remaining cases, since no histology was available for confirmation and some at least may represent naevi rather than melanomas.

Despite limited follow-up in some patients in our series two of our patients developed metastatic disease, illustrating the potential mortality of enlarging iris melanomas. Early excision before there is invasion of the ciliary body or extrasceral extension would appear to be preferable. Early removal should require less radical surgery than late removal and therefore preserve vision with least complication while removing the malignant focus. This implies the need for close follow-up of the lesions for evidence of growth.

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Anterior chamber lens implantation after vitreous loss*

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SUMMARY Vitreous loss is a serious complication of cataract surgery. Following vitreous loss it is common practice to perform a primary implantation of an anterior chamber lens (AC-IOL). We retrospectively analysed 642 consecutive cases of cataract extraction performed between 1983 and 1986 with special attention to those patients in whom vitreous loss occurred and an AC-IOL was placed. There were 27 such cases, and 24 of these were available for follow-up. Eighteen (75%) had visual acuity of 20/40 or better. All six patients (25%) who had a visual acuity of less than 20/40 in the operated eye had a functional visual acuity of 20/200 or less. Complications that occurred in this group are discussed. We are concerned that the complications associated with vitreous loss and with AC-IOLs may be acting in concert to cause visually disabling results.

Vitreous loss is a well known complication of cataract surgery. Following vitreous loss there is an increased risk of retinal detachment, expulsive haemorrhage, cystoid macular oedema, corneal decompensation, and secondary glaucoma.¹ The visual outcome in these patients is compromised.^{2,3} After vitreous loss occurs it is common practice to do a partial anterior vitrectomy and then place an anterior chamber lens (AC-IOL). Reports on the effect of placing an AC-IOL after vitreous loss have concluded that in experienced hands it is a safe procedure.⁴⁻⁶ However, these reports do show that patients who receive an AC-IOL after vitreous loss do significantly less well than those patients who receive a posterior chamber intraocular lens (PC-IOL) after straightforward extracapsular cataract surgery. The contribution of the AC-IOL to this diminished success is unclear at present. One of us (TJS) has been particularly struck by the magnitude of the problems induced by AC-IOLs as seen in a referral glaucoma practice. To estimate the incidence of severe complications following AC-IOL placement after vitreous loss we reviewed all of the cataract extractions performed at the Veterans Administration Hospital in Lexington,

Kentucky, from 1983 through 1986 with special attention to those patients in whom vitreous loss occurred and an AC-IOL was placed.

Results

Six hundred and forty-two consecutive cataract extractions performed between 1983 and 1986 were reviewed. There were 27 instances of vitreous loss with anterior chamber lens insertion (4.4%); 24 (89%) were available for follow-up ranging from three months to more than four years. Of the 24 patients who had an AC-IOL placed after vitreous loss 18 (75%) had a visual acuity of 20/40 or better. However, of the six patients (25%) who had a visual acuity of less than 20/40 in the operated eye all had functional visual acuity of 20/200 or less. Five of the six patients had a Kellman multiflex MT4 or MT5 manufactured by Cilco implanted. Patient no. 5 had a Cilco AC2 implanted. Complications that occurred in this group leading to the poor visual outcome are summarised in Table 1.

Case reports

Case 1. A 70-year-old white male with a history of corneal breakdown from probable herpetic infection in 1945 presented with initial VA of hand motion OD. He was noted to have a deep, crater-like, non-

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Table 1 Breakdown of the complications following vitreous loss and implantation of an anterior chamber intraocular lens

Case	Complications	Uveitis	Corneal decomp.	IOP eleva-tion	Retinal Detach-ment	Lens malposi-tion	CME	VA
1				X			X	20/200
2			X				X	CF
3	X	X	X			X	X	CF
4	X				X	X	X	CF
5					X	X		NLP
6	X	X	X	X	X	X	X	20/200

IOP=intraocular pressure. CME=chronic cystoid macular oedema. VA=visual acuity. CF=counting fingers. NLP=no light perception.

ulcerative lesion with deep stromal scarring of the cornea OD. A penetrating keratoplasty was performed in combination with an attempted extracapsular cataract extraction (ECCE), which was complicated by vitreous loss. After a partial anterior vitrectomy an AC-IOL was placed. During a follow-up period of two years he never attained a visual acuity better than 20/200 with correction. He had pupillary block glaucoma which led to chronic angle closure. In addition he suffered from chronic cystoid macular oedema. At the last follow-up, 27 months after surgery, he had a best corrected visual acuity of 20/200.

Case 2. A 77-year-old white male with a history of a corneal ulcer from a chemical burn in 1943 presented two years after a penetrating keratoplasty with an initial visual acuity of 20/200 OS. He underwent an ECCE which was complicated by vitreous loss. After a vitrectomy an AC-IOL was inserted. During the follow-up period of three years his visual acuity was never better than 20/300. His course was complicated by graft failure and cystoid macular oedema. Two repeat penetrating keratoplasty procedures were performed. At the last follow-up he had a visual acuity of counting fingers at 1 m, 2–3+ cystoid macular oedema, and 2+ corneal oedema, with graft rejection.

Case 3. A 63-year-old white male presented with no significant medical history and a best corrected visual acuity with a pinhole of 20/70 OS. He underwent an ECCE, which was complicated by vitreous loss and had primary implantation of an AC-IOL. During a follow-up period of four years his course was complicated by chronic iritis, corneal oedema, vitritis, and a raised IOP. His best postoperative visual acuity was 20/200. He had 3–4+ inflammatory deposits on the IOL and had a peaked iris with atrophy secondary to haptic traction on the iris. Eleven months after surgery the inferior haptic was in

the iris and the superior haptic was floating free. A cellophane maculopathy was present, and the IOL was subsequently removed. At his last follow-up the visual acuity was counting fingers at 60 cm. He had 4+ cystoid macular oedema, diffuse corneal oedema, and an unstable intraocular pressure.

Case 4. A 68-year-old white male presented with an initial visual acuity of 20/400. He underwent an ECCE complicated by vitreous loss and had an AC-IOL placed. His initial postoperative course was complicated by persistent iritis and vitreous haemorrhage. The superior footplates of the lens were noted to be in the iris at three months. At six months he was noted to have cystoid macular oedema and vitreous haemorrhage, and the IOL was subsequently removed. Twenty-five months after the operation he had a retinal detachment, which was successfully repaired. At his last follow-up 35 months after surgery he had a visual acuity of counting fingers at 60 cm.

Case 5. A 71-year-old white male presented with an initial visual acuity of light perception OS. He underwent an ECCE OS complicated by vitreous loss and had an AC-IOL placed. His initial postoperative visual acuity was 20/70 with a pinhole. The eye was subsequently found to be hypotonous and inferior choroidals were present. Visual acuity decreased to counting fingers at 60 cm. Three months after operation he suffered a retinal detachment. Following repair the diagnosis of 'tight lens syndrome' and pupillary block was made, and the lens was removed. His subsequent course was complicated by rubeosis and progression to a total, inoperable retinal detachment. He had a retrobulbar block for pain control two years after surgery. At his last follow-up the visual acuity was no light perception OS.

Case 6. A 67-year-old white male presented with an initial visual acuity of 20/100. He underwent an ECCE complicated by vitreous loss, and an AC-IOL was inserted. Initial postoperative examination showed a 10% hyphaema. The pupil was slightly irregular, and his intraocular pressure was increased. The visual acuity was 20/200. His subsequent postoperative course was notable for multiple complications including malpositioning of the IOL, retinal detachment requiring surgical repair, chronic iritis, and chronic cystoid macular oedema. At his last follow-up visit he had a visual acuity of 20/200, 3+ guttae, and early bullous keratopathy. One of the IOL haptics was located in a peripheral iridotomy, and the IOL itself was covered with pigment.

Discussion

Vitreous loss at the time of surgery can lead to visual impairment. Early reports demonstrate the compli-

cations that can result from vitreous loss.⁷⁻⁹ Although modern management has improved on these results, patients on whom vitreous loss occurs still do less well than patients who do not have this complication.^{2,3} Kasner and Jaffe¹⁰ reported the results on 105 patients with vitreous loss treated by a partial anterior vitrectomy. In this group 81% had a visual acuity of 20/50 or better. Only 10.5% had vision of 20/100 or worse.

The role that placement of an AC-IOL after vitreous loss has on the incidence of complications and resultant visual outcome has not been clearly established. Jaffe⁵ reported on 88 patients who received IOLs after vitreous loss. Visual acuity was better than 20/40 in about 80% of them. He concluded that IOL placement after vitreous loss was justified if the surgeon was experienced and that the incidence of complications was not high enough to contraindicate lens implantation. All but one of the IOLs used in this retrospective study were the Binkhorst iris clip lens, which has now become obsolete. Mazzocco⁴ reported a series of 38 patients who had IOLs placed after vitreous loss. Twenty-three of these had the Choyce mark VIII placed; in these he noted an increased incidence of glaucoma. Nine of the 23 had glaucoma; all were medically controlled. He came to the same conclusion as did Jaffe. Nishi⁶ reported on 18 patients who had IOLs placed after vitreous loss. He used both anterior and posterior chamber lenses. The final visual acuity in this group ranged from 20/60 to 20/15, while in his control group it was 20/50 to 20/15. He also concluded that placement of an IOL after vitreous loss was not contraindicated.

This series consists of 24 consecutive patients in whom an AC-IOL was placed after vitreous loss and for whom at least three months of follow-up is available. Eighteen of the patients (75%) achieved a visual acuity of 20/40 or better, which is in fairly close agreement with Jaffe's results⁵ and similar to that found after vitreous loss alone.^{2,3} The remaining six patients, however, had multiple complications and a poor visual outcome (visual acuity 20/200 or worse). Some of these patients had complications directly attributable to the AC-IOL, which we believe may have contributed to their poor visual results.

Several of the complications known to occur after vitreous loss are also seen with the use of anterior chamber lenses. Glaucoma, uveitis, and corneal disease are all increased after vitreous loss. These complications are also seen with the use of an AC-IOL in uncomplicated surgery.¹¹ Mazzocco's results⁴ indicate that there may be a combined effect of the two in the case of glaucoma, but no other study indicates that vitreous loss and an AC-IOL combined yield a significantly increased risk of these complica-

tions. Three of the patients reported on here (cases 1, 3, and 6) suffered from increased intraocular pressure. In case 1 this was caused by a pupillary block mechanism; the iris was noted to be prolapsing round the lens despite the presence of a peripheral iridectomy. Peripheral anterior synechiae were present. Case 3 had open-angle glaucoma thought to be secondary to chronic iritis, possibly from a malpositioned lens. Three patients (cases 3, 4, and 6) had uveitis. In all of these cases the lens was impinging on the iris. Three of the patients had evidence of corneal decompensation (cases 2, 3, and 6). Case 3 had diffuse corneal oedema after removal of the IOL. This may have been secondary to chronic uveitis or the trauma of lens removal.

An increased risk of retinal detachment follows vitreous loss.¹¹⁻¹⁴ While there is no evidence that the use of an IOL increases this risk, the presence of an AC-IOL may make reattachment of the retina more difficult. Three patients had a retinal detachment (cases 4, 5, and 6). In case 4 this occurred several months after the removal of the IOL. In patient 5 the detachment was thought to be inoperable, and the visual acuity progressed to no light perception.

The incidence of cystoid macular oedema is increased after vitreous loss.¹ Whether an IOL alone increases the risk of this complication is not well established. Jaffe's results⁵ seem to indicate an increased risk in those patients with an iris supported lens, but we are not aware of any study of anterior chamber lenses in association with this complication. Five of our patients had evidence of cystoid macular oedema (cases 1, 2, 3, 4, and 6).

We are concerned about the poor visual outcome in those patients who had complications following vitreous loss and placement of an AC-IOL. As in other series, however, the number of patients is very small. We do not think that a general statement concerning the safety of this practice would be valid. More than a million cataract extractions are performed every year in the United States alone¹⁵; tens of thousands will suffer the complication of vitreous loss. We believe the complications associated with vitreous loss and AC-IOLs may be acting in concert to cause visually disabling results in some of these patients and that a large prospective study is warranted to delineate the effect an IOL has after vitreous loss. If the incidence of complications is proved to be increased, the surgeon and patient will be better able to weigh the benefits of an IOL after vitreous loss against the possible risk.

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Penetration of 2% cyclosporin eyedrops into human aqueous humour

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SUMMARY The penetration into the eye and the systemic absorption of 2% cyclosporin eye drops were determined by polarisation immunofluorescent assay of cyclosporin in the aqueous humour and plasma of 30 patients at the time of cataract surgery. The results were then compared with the corresponding results after oral administration at a dosage of 5 mg/kg/day to three further patients. The maximum intraocular concentration (24 (SD 9) mg/l) was achieved four hours after topical administration. This level was slightly less than that found in aqueous humour (28 (SD 10) mg/l) 12 hours after systemic administration of the drug at a dosage of 5 mg/kg/day. Both these levels are below the minimum therapeutic level (50-100 mg/l). Topical application of cyclosporin A did not produce detectable levels in plasma at any time. These results indicate that the efficacy of cyclosporin A in the control of intraocular inflammation is attributable to its systemic immunoregulatory effect rather than to the local ocular effect.

Cyclosporin A is a drug which exerts a potent selective immunosuppressant effect on certain functions of T lymphocytes in the cell-mediated immune response.¹ It has proved to be very effective in the treatment of cases of severe endogenous uveitis refractory to other drugs such as corticosteroids and other immunosuppressants (azathioprine, chlorambucil, and others).² The systemic administration of cyclosporin A even at dosages as low as 5 mg/kg/day is, however, associated with some well known side effects, in particular nephrotoxicity, arterial hypertension, gingival hypertrophy, and hypertrichosis.³

It is not yet known whether the efficacy of cyclosporin A is due to its systemic action on the immune system or whether it is due to its regulatory action on immunoreactive cells at the local ocular level. In a large number of animal experiments cyclosporin A has proved effective in prolonging the survival time of corneal grafts whether administered via the subconjunctival,⁴ retrobulbar,⁵ intramuscular,⁶ or topical⁷ routes. This suggests that the effect of cyclosporin A is due principally to a local immunoregulatory effect at the ocular level rather than to a systemic effect.

Local administration of cyclosporin A as 2% eye-

drops has also proved to be effective both in preventing and in controlling the progression of experimental autoimmune uveitis induced by retinal S-antigen, provided always that therapeutic plasma levels are achieved.⁸ This suggests that the therapeutic action of cyclosporin A is due to its systemic immunoregulatory effect rather than to its local ocular effect.

The aim of the present study was to determine the extent of penetration of cyclosporin A into human aqueous humour and serum after local ocular administration of 2% eyedrops, since this information, which is not yet known, is essential in order to establish the mechanism of action of this drug on ocular inflammation.

Material and methods

A 2% solution of cyclosporin in olive oil was used for topical administration.

After a detailed explanation to each patient of the purpose of the study, two drops (100 µl) of 2% cyclosporin solution (20 g/l) were applied to one eye every six hours—the treatment starting 72 hours before cataract surgery—to a total of 30 patients aged between 59 and 71 years.

Aqueous humour (0.15-0.20 ml) was obtained by aspiration of the anterior chamber with a 25-G needle

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at the following times after the final topical application of the drug: ½ an hour in five patients, 2 hours in five patients, 3 hours in five patients, 4 hours in five patients, 5 hours in five patients, and 12 hours in five patients. All these times corresponded to the start of cataract surgery.

A specimen of plasma was obtained at the same time as the aqueous humour, and both specimens were then assayed by polarisation immunofluorescence (Abbott) for cyclosporin A content.

Three further patients were given a once daily oral dose of 5 mg/kg/day of cyclosporin A, the treatment starting one week before cataract surgery. The specimens of aqueous humour and plasma were taken simultaneously at the time of surgery and 12 hours after oral administration of the drug, and the level of the drug in both specimens was determined.

Results

The individual plasma and intraocular concentrations of cyclosporin A after topical therapy with 2% cyclosporin are shown in Table 1. The peak concentration in aqueous humour (24 SD 9) mg/l) was achieved four hours after application of the solution. The level then declined progressively until at 12 hours after the final application cyclosporin A was no longer detectable. At no stage was the drug identified in the plasma.

The three patients who received 5 mg/kg/day of cyclosporin A orally had plasma levels of 247, 161, and 210 mg/l respectively 12 hours after administration. The corresponding levels in aqueous humour

were 28, 20, and 36 mg/l respectively (mean 28 (SD 10) mg/l) (Table 2). These levels are similar to those found four hours after topical administration of the 2% solution of cyclosporin A.

Discussion

Cyclosporin A is a neutral hydrophobic cyclic peptide. The corneal epithelium is also hydrophobic and is therefore easily penetrated by lipid soluble substances such as cyclosporin A. The corneal stroma, in contrast, is hydrophilic and therefore does not permit the passage of a hydrophobic drug such as this. Topically applied cyclosporin A easily penetrates the corneal epithelium and accumulates in the stroma, only very small amounts passing into the aqueous humour.

This was demonstrated by Mosteller and associates,⁹ who applied a total topical dose of 3 mg/kg/day of cyclosporin A to rabbits. This resulted in levels of more than 900 mg/l in corneal tissue three hours later, whereas the concentration in aqueous humour was less than one-thirtieth of this.

Topical administration of cyclosporin A has been proposed as an alternative to systemic in the treatment of uveitis which would avoid the appearance of side effects (nephrotoxicity, arterial hypertension, etc.). This idea appeared to be supported by a number of animal experiments, in all of which topical application of cyclosporin A achieved plasma levels within the range regarded as therapeutic (50–300 mg/l),¹⁰ even though this level was not reached in the aqueous humour. The application of 2% cyclosporin

Table 1 Concentration of cyclosporin A in human aqueous humour following application of 2% cyclosporine eyedrops

No. of hours after application	Number of specimens	Concentration in aqueous humour (mg/l)	Concentration in plasma (mg/l)
½	5	0	0
2	5	6 (SD 3)	0
3	5	12.5 (SD 5)	0
4	5	24 (SD 9)	0
5	5	16 (SD 7)	0
12	5	0	0

Table 2 Concentration of cyclosporin A in aqueous humour following once daily administration of 5 mg/kg/day orally

No. of hours after application	Number of specimens	Concentration in aqueous humour (mg/l)	Concentration in plasma (mg/l)
12	1	28	247
12	1	20	161
12	1	36	210
		28 (SD 10)	204 (SD 43)

Table 3 Comparison of the levels of cyclosporin A in aqueous humour and plasma in relation to different topical administration protocols in various species

Study	Species	Type and route of administration	Dose of cyclosporine (mg/kg/day)	Hours since administration	Concentration in aqueous humour (mg/l)	Concentration in plasma (mg/l)
Mosteller <i>et al.</i> ⁹	Rabbit	10% ointment	3	4	62	75
Nussenblatt <i>et al.</i> ⁸	Rat	2% eyedrops	40	4	—	285
Bell and Hunisett ¹¹	Rabbit	1% eyedrops	2.5	—	27	116
Present study	Man	2% eyedrops	0.11	4	24	0

eye drops to rats by Nussenblatt and associates,⁸ for example, resulted in plasma levels of 285 and 108 mg/l following doses of 40 and 10 mg/kg/day respectively. These concentrations of the drug are effective as prophylaxis and therapy of experimental autoimmune uveitis (EAU) induced by retinal S-antigen. Topically applied cyclosporin A was effective against EAU only if therapeutic levels (50–300 mg/l) were reached, but in such cases it was effective even with very low, subtherapeutic, intravitreal levels (19 mg/l). This observation suggests that the principal mechanism of action of cyclosporin A in controlling severe ocular inflammation is not so much its local ocular effect but rather its systemic effect on the immune system, in that by blocking the production of interleukin 2 (IL-2) it interrupts the entire lymphokine cascade. However, the demonstrated efficacy of intracamerally administered cyclosporin A against EAU suggests that the drug also exerts a local ocular effect.

The topical administration of 3 mg/kg/day of cyclosporin A to rabbits by Mosteller and associates⁹ resulted in plasma and aqueous humour levels of 75 and 62 mg/l respectively four hours later.

Bell and Hunisett¹⁰ applied a topical dosage of 2.5 mg/kg/day of cyclosporin A to rabbits and found levels of 116 mg/l in plasma and 27 mg/l in the aqueous humour. This plasma level produced a level of 18 mg/l in the aqueous humour of the contralateral eye.

Given that the ocular surface area of rats and rabbits is incomparably larger in relation to body weight than it is in man, it is not surprising that the topical administration of cyclosporin A should result in therapeutic plasma levels in these animals.

The topical therapy protocol which we used in humans was very similar in terms of concentration, dose, and frequency of administration of cyclosporin A to that used in previous animal studies.^{8,11} This meant that the total dose of cyclosporin A for a 70 kg individual was only 0.11 mg/kg/day; hence it is not surprising that cyclosporin A was not detectable in plasma. The peak concentration in aqueous humour (24 (SD 9) mg/l) was reached four hours after administration. These low intracameral levels together with the absence of therapeutic plasma concentrations (0 mg/l) account for the fact that 2% cyclosporin eyedrops are ineffective either in endogenous posterior and intermediate uveitis or even in anterior uveitis, this fact being confirmed by our own clinical experience. Table 3 shows a comparison of the levels of cyclosporin A in aqueous humour and plasma in various species in relation to different administration protocols.

The low intraocular levels of cyclosporin A produced by either topical or systemic administration

contrast with the high concentrations of the drug in other tissues such as lymph nodes, for example, in which the level may be 10 times higher than in plasma.¹²

The use of a different vehicle (for example, liposomes) or clinical trials with solutions of higher concentrations (for example, 10%) may produce therapeutic levels (>50 mg/l) in the aqueous humour and thus make it possible to establish precisely what local immunoregulatory effect is exerted by cyclosporin A in endogenous anterior uveitis.

The ratio (0.14 (SD 0.03)) of the level of cyclosporin A found in human aqueous humour to that in plasma 12 hours after systemic administration of low doses (5 mg/kg/day) was lower than that found by Palestine and associates¹³ (0.40 (SE 0.24)) 24 hours after local administration of the drug. The actual level was slightly higher than that found four hours after topical administration. This fact can be regarded as strong evidence for the hypothesis that the principal action of cyclosporin A in endogenous uveitis is a systemic immunosuppressant effect rather than a local intraocular immunoregulatory effect. We consider that larger scale studies are required in order to determine precisely the nature of the immunoregulatory action of cyclosporin A at the local and systemic levels in the treatment of intraocular inflammation.

We conclude that topical administration of 2% cyclosporin eyedrops produces subtherapeutic levels of cyclosporin in the aqueous humour and undetectable levels in plasma. Systemic administration of cyclosporin A at a dosage of 5 mg/kg/day produced subtherapeutic levels in aqueous humour, but therapeutic levels in plasma. We conclude from this investigation that the principal action of cyclosporin A on intraocular inflammation is a systemic one on the immune system rather than a local immunoregulatory action at the ocular level, and therefore that the use of 2% cyclosporin eyedrops cannot be regarded as a satisfactory treatment of refractory anterior uveitis.

We express our thanks to Dr R B Nussenblatt for introducing us to the use of cyclosporin A.

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Bromovinyldeoxyuridine and interferon treatment in ulcerative herpetic keratitis: a double masked study

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SUMMARY Bromovinyldeoxyuridine is a potent and safe antiherpes compound that in combination with a placebo treatment promoted the partial and complete healing of herpetic epithelial disease in 22 patients in average times of 4.6 days and 8.5 days respectively. However, when BVDU was combined with 1.5×10^6 IU of recombinant $\alpha 2C$ interferon, partial and complete healing times for keratitis in 19 patients were reduced to 2.6 days and 4.6 days respectively. No toxic effects of the medications were observed in any patient.

Bromovinyldeoxyuridine ((*E*)-5-(2-bromovinyl)-2'-deoxyuridine, BVDU) is a 5-substituted analogue of 2'-deoxythymidine (dThd),¹ like idoxuridine (5-iodo-2'-deoxyuridine, IDU) and trifluorothymidine (5-trifluoromethyl-2'-deoxyuridine, TFT). Studies *in vitro* have shown BVDU to possess a more potent and selective activity against herpes simplex virus type 1 (HSV-1) than IDU, TFT, and several other antiviral agents, namely, vidarabine (9- β -D-arabinofuranosyladenine, ara-A, Vira-A), acyclovir (9-(2-hydroxyethoxymethyl)guanine, acycloguanosine, ACV, Zovirax), and foscarnet (phosphonoformate).^{2,4} Other viruses sensitive to BVDU are varicella-zoster virus (VZV),^{5,6} simian varicella virus,⁷ Epstein-Barr virus, and some viruses of veterinary importance, namely, suid herpesvirus type 1 and bovid herpesvirus type 1.⁸

BVDU inhibits the replication of HSV-1^{3,4} and VZV^{5,6} at very low concentrations (0.001-0.01 mg/l), whereas the cell toxicity is observed only at drug concentrations of 50-100 mg/l. The selective antiviral activity of BVDU is based on its mechanism of action. In virus infected cells the HSV-1- and VZV-encoded thymidine kinases specifically phosphorylate BVDU.^{9,10} Once converted to its 5'-triphosphate form, BVDU inhibits viral DNA polymerases in a competitive fashion with regard to 2'-deoxythymidine triphosphate (dTTP). BVDU 5'-triphosphate (BVDUTP) has a much greater affinity for HSV-1 DNA polymerase than for the

cellular DNA polymerases α , β , and γ .¹¹ BVDUTP also serves as an alternative substrate for viral DNA polymerase,¹² which results in its incorporation, as BVDU 5'-monophosphate (BVDUMP), into the viral DNA.¹³ The HSV-2-encoded dThd kinase is less efficient in phosphorylating BVDU.^{10,14} Consequently the drug is less effective against HSV-2. BVDU is also inactive against dThd kinase-deficient (TK⁻) mutants of HSV.

Studies on experimental animals have shown topically administered BVDU to be significantly better than IDU in suppressing the development and promoting the healing of epithelial keratitis,^{15,16} and superior to TFT in suppressing the development of HSV-1 stromal disease.¹⁷ Iritis and endotheliitis, produced by directly inoculating the virus into the anterior chamber of rabbit eyes, responded better to BVDU eyedrops than TFT eyedrops.¹⁸ (¹²⁵I)IDU, a radiolabelled analogue of BVDU, readily penetrates the normal rabbit cornea on topical application and attains therapeutic concentrations in the aqueous humour.¹⁹

Both short-term^{20,21} and long-term^{22,23} follow-up studies in a clinical setting have established that BVDU is a safe and efficacious compound for the treatment of HSV-1 dendritic keratitis, geographic ulcers, and stromal keratitis. The present study was aimed at investigating whether combined therapy of topical BVDU eyedrops and interferon would induce a faster healing of dendritic keratitis than BVDU eyedrops alone. Combination therapy of antiviral

drugs (namely, TFT and ACV) with interferon has proved to promote faster healing of herpetic keratitis than the antiviral agents used alone.²⁴⁻²⁶

Materials and methods

Patients who presented with a recent recurrence of epithelial herpetic keratitis, without associated complications such as stromal disease, iritis, or secondary glaucoma, were included in the study. Typical dendritic ulcers were present in 30 patients, three patients had stellate lesions, and eight patients had small geographic ulcers. Informed consent was obtained from each patient, or from the parents in the case of children, following the declaration of Helsinki.

The trial was conducted in a double-masked randomised fashion. Before treatment was started material for virus culture was obtained from the corneal lesions by minimal wiping.

Treatment consisted of either BVDU 1% ointment in Fischer's ointment base and recombinant human α 2C interferon (rHuIFN) 1.5×10^6 IU IFN as a solid, soluble substance delivered by an ophthalmic rod, or BVDU 1% ointment and placebo in the form of 3% human serum albumin on an ophthalmic rod. BVDU ointment was applied five times a day. The first application was given after either the interferon or the placebo treatment and was administered daily in the outpatient department of the hospital. This treatment schedule was continued until complete healing of keratitis was achieved, whereafter BVDU ointment alone, five times a day, was applied for another six days.

Two criteria were used to define healing of keratitis, namely, partial healing, when the epithelial wound was closed, and complete healing, which meant an absence of intraepithelial cysts or epithelial oedema in addition to wound closure.

The time required to accomplish partial or complete healing by two treatment regimens was recorded, and the data were subjected to analysis of variance.

Results

The characteristics of the patients in the BVDU- α rHuIFN and the BVDU-placebo groups are shown in Table 1. The two treatment groups were comparable in terms of age and sex. The type and size of corneal lesions and the duration of symptoms before treatment was initiated did not differ significantly in the two groups (Table 2).

Nineteen patients received BVDU- α rHuIFN therapy (Table 3). Partial healing of keratitis occurred in this group in an average of 2.6 days and

Table 1 Patient characteristics of the bromovinyldeoxyuridine-recombinant human α 2C interferon (BVDU-rHuIFN) and the BVDU-placebo treatment group

Patient characteristics	BVDU+ rHuIFN	BVDU+ placebo	Significance
Sex male %	47	59	NS
female %	53	41	
Age median	32	45	NS
range	7-32	12-81	
Affected eye % OD	53	45	NS
OS	47	55	

NS: not significant.

Table 2 Interval in days between the occurrence of the first symptoms and the beginning of treatment

	BVDU-rHuIFN	BVDU-placebo
Mean (hours)	48	36
Average (days)	6.6	5.6
SD (n-1)	5.0	4.7
n	19	22

BVDU: bromovinyldeoxyuridine.

rHuIFN: recombinant human α -2C interferon.

SD: standard deviation.

n: number of patients.

Table 3 The average number of days for partial and complete healing of herpetic keratitis with BVDU-rHuIFN and BVDU-placebo treatment

		Healing	
		Partial	Complete
BVDU-rHuIFN	x	2.6	4.5
	n	19	19
	SD (n-1)	0.9	1.4
BVDU-placebo	x	4.6	8.5
	n	22	22
	SD (n-1)	1.3	2.2
Significance (p)		0.001	0.001

BVDU: bromovinyldeoxyuridine.

rHuIFN: recombinant human α -2C interferon.

x: mean.

n: number of observations.

SD: standard deviation.

complete healing in an average of 4.5 days. The 22 patients on the BVDU-placebo regimen showed partial healing in an average of 4.6 days and complete healing in an average of 8.5 days.

The distribution of days for partial healing in the BVDU-placebo group showed a tendency to right skewness ($\beta_1=0.23$), whereas this distribution was almost symmetrical ($\beta_1=0.0001$) in the BVDU-rHuIFN treatment group. Both of these distributions were platykurtic, that is, more widely dispersed from

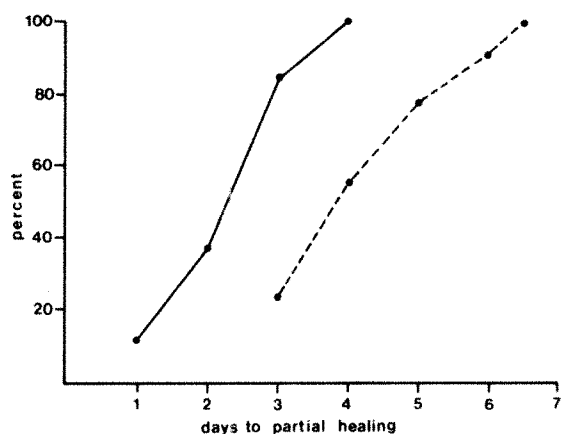


Fig. 1 Cumulative frequency distribution for partial healing of herpetic keratitis treated with bromovinyldeoxyuridine and recombinant human $\alpha 2C$ interferon (●—●) or with bromovinyldeoxyuridine and placebo (●---●).

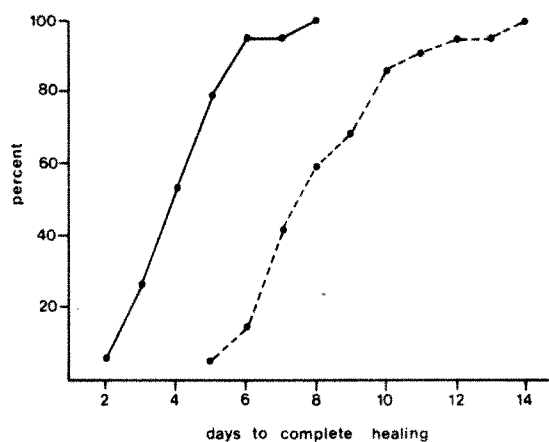


Fig. 2 Cumulative frequency distribution for complete healing of herpetic keratitis treated with bromovinyldeoxyuridine and recombinant human $\alpha 2C$ interferon (●—●) or with bromovinyldeoxyuridine and placebo (●---●).

the mean than normal, resulting in a broad and flattened distribution curve. As regards complete healing, the distributions of days for BVDU-placebo and BVDU-rHuIFN treatments were slightly skewed to the right (β_1 value 0.59 and 0.23, respectively) and leptokurtic—less widely dispersed from the mean than normal—resulting in a higher and narrower distribution curve.

Graphic presentation of the cumulative frequency distributions for the partial and complete healing times are shown in Figs. 1 and 2. Statistical analysis of the data showed a highly significant difference (Table 3, $p < 0.001$) between both the complete and partial healing times of the two treatment groups.

Discussion

The present study shows that a combination therapy of α rHuIFN and BVDU leads to the healing of herpetic keratitis in about half the time required on combined BVDU-placebo treatment. Interferon in combination with other antiviral drugs (TFT^{24,25} or ACV²⁶) has been reported to promote a significantly faster healing than these antivirals used alone. It is still not clear how interferon achieves this beneficial effect when given in combination therapy, as interferon monotherapy does not seem to have any clinical value in the treatment of herpetic dendritic ulcers.²⁷

The average healing time of 8.5 days obtained with BVDU-placebo therapy in the present study is similar to the healing time (average 8.6 days in 76 cases of dendritic ulcers) obtained from treatment with BVDU 0.1% eyedrops, instilled nine times a

day, in a large series of patients.²³ The use of BVDU 1% ointment did not promote a shorter healing time than BVDU 0.1% eyedrops, which confirms the experimental data that increasing the concentration of BVDU in ointment from 0.1% to 2.5% did not improve the therapeutic efficacy of the drug.¹⁶ These observations also suggest that at a 0.1% concentration BVDU appears to be adequate to achieve an optimal therapeutic effect, whether the drug is delivered in the form of eyedrops or ointment.

In our trial we included only those patients who had uncomplicated herpetic epithelial disease of recent onset and had not been treated with other antiviral drugs. In a reported study^{23,44} of 76 patients with dendritic keratitis failed to respond to other antiviral drugs, namely, IDU, TFT, Vira-A, Zovirax, before their treatment was switched to BVDU eyedrops. Since all these patients healed rapidly (average 8.6 days) under BVDU topical eye drops it appears that this drug is an efficacious compound whether the treatment is started early, as in our study, or late, as reported previously.²³

Except for hypersensitivity reactions to the topical drug formulation in a small number of patients, which may be attributed to the vehicle rather than the drug, no other toxic side effects have been reported.²³ In the present investigation no toxic effects, including drug allergy, were observed.

Since BVDU is a selective, safe, and effective compound, it may be used in combination with interferon to achieve a rapid healing of herpetic epithelial disease. Our patients accepted the dispensing of freeze-dried recombinant human $\alpha 2C$ interferon delivered by an ophthalmic rod readily

and rapidly learned how to administer the drug combination. This is of great practical importance, as the patients would not have to visit the ophthalmologist daily if such treatment was prescribed on a routine basis.

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Trabeculectomy versus trabeculotomy in congenital glaucoma

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SUMMARY Congenital glaucoma is one of the main causes of blindness in children and is more common in Saudi Arabia than in Western countries, perhaps owing to the prevalence of consanguinity with families. Trabeculotomy has given poorer results in Saudi Arabia than elsewhere. This study compared the results of trabeculotomy (67% success rate) with trabeculectomy (54% success rate), and reports fewer complications following trabeculotomy.

Congenital glaucoma occurs in 1:10 000 births in Western societies¹⁻⁴ and is commoner in Saudi Arabia, with a reported frequency of 1:2500.¹ Among all ophthalmic patients in the Western countries this accounts for 0.1–0.4% of all conditions and in institutions for the blind; 2–15% of patients have congenital glaucoma.¹ In Saudi Arabia it accounts for 16% of all blindness in children.⁶

Most cases appear to be sporadic, but 10% are familial. Most of these cases show transmission by an autosomal recessive trait, but dominant types have been described. It seems likely that in Saudi Arabia most cases are inherited owing to the social pattern of marrying within families.²

Various surgical procedures have been described for the management of congenital glaucoma. Goniotomy and trabeculotomy have proved most popular, with the success rate of 80–93% in Western societies.⁷⁻⁹ Trabeculectomy on the other hand has proved less successful, having a variable success rate and more serious complications.¹⁰⁻¹⁴

There has been no study directly comparing the results of trabeculotomy with trabeculectomy for congenital glaucoma. A retrospective study was therefore made to compare two groups of children treated by each method. There was no obvious selection involved, since one surgeon preferred trabeculotomy, while the other preferred trabeculectomy, with children being referred to one or other without prior knowledge of the surgery intended.

The success of the procedure was measured by reduction of the intraocular pressure to, or below, 16 mmHg as measured by applanation tonometry under general anaesthesia and without additional medica-

tion. Normal values for intraocular pressure were based on a previous study in Saudi children under general anaesthesia,¹⁵ in which 33 consecutive non-glaucomatous children were examined, from birth to 6 years of age, who were having a variety of other ophthalmic surgical procedures such as probing and syringing of the nasolacrimal duct, surgery for lid chalazion, strabismus, ptosis, and lens aspiration.

The mean intraocular pressure by hand held Perkins tonometer was 10.2 (range 6–15) mmHg and by Schiøtz tonometer 12.5 (range 5.9–20.6) mmHg. The distributions of these values were calculated to give valid reference ranges of 4–16 mmHg for the applanation tonometer and 3–22 mmHg for the Schiøtz tonometer.¹⁵

Patients and methods

The retrospective study covered all cases of congenital glaucoma treated at Riyadh Armed Forces Hospital from January 1981 to April 1988. Each patient's age, sex, family history, and consanguinity history were noted, and each underwent a careful ocular examination under general anaesthetic (halothane, nitrous oxide, and oxygen). The patient's corneal diameter, corneal integrity, and intraocular pressure (IOP) measurement both with Perkins hand held tonometer and then Schiøtz tonometer were recorded. In addition retinoscopy, gonioscopy, and funduscopy were performed when the media was clear. Children with proved congenital glaucoma underwent either trabeculectomy or trabeculotomy under general anaesthesia according to the surgeon's choice irrespective of the IOP recorded.

The surgical technique used for trabeculectomy was basically that of Cairns.¹⁶ A limbal-based conjunctival flap was prepared in the superior quadrant. Underlying Tenon's capsule was then dissected from episclera and excised generously. A thin, rectangular, partial-thickness scleral flap measuring approximately 4×4 mm was prepared by dissecting well forward into clear cornea. A 2×2 mm section of deep limbal tissue was excised from beneath the base of the rectangular flap. A small peripheral iridectomy was then performed beneath the fistula. The scleral flap was approximated with two 10-0 nylon sutures, and the conjunctival incision was closed with a tight running suture of 8-0 Vicryl. The eye was dressed with mydriatics and an antibiotic-corticosteroid ointment at the end of the procedure.

The surgical technique followed for trabeculotomy *ab externo* was that of McPherson.¹⁷ A limbal-based conjunctival flap was fashioned in the superior quadrant of the operated eye. A thin limbal-based partial thickness scleral flap measuring approximately 4×2 mm was dissected down to the corneo-scleral limbus. A 2 mm radial incision was then made at the corneoscleral transition zone, where the Schlemm's canal lay. To confirm the canal's identity a 5-0 nylon suture was threaded through the cut edge. The exposed portion of suture was then bent up and down, it being noted whether it returned to a position parallel to the canal when released. Its failure to do so suggested that a false passage may have been created into the anterior chamber or supraciliary space.

One arm of a McPherson's trabeculotome was then threaded into Schlemm's canal with the other parallel arm as a guide. The handle was then rotated, so that the arm within the canal tore through the trabecular meshwork into the anterior chamber. The same procedure was then performed on the other side of the radial incision. The scleral and conjunctival incision was then closed with 10-0 nylon and 8-0 Vicryl suture respectively. Mydriatics and antibiotic-corticosteroid ointment was used for dressing at the end of the procedure.

Interoperative and postoperative complications were recorded, and the children were followed up at regular intervals by examining them under general anaesthesia with the same anaesthetist whenever possible. Each examination included recording the corneal diameter, corneal integrity, intraocular

pressure level, results of retinoscopy, and disc pathology.

Results

Between January 1981 and April 1988, 42 Saudi children with congenital glaucoma were treated. Ten patients were excluded from the study either because of short follow up, multiple operations, or partial treatment in other hospitals. There were 18 male and 14 female children. Twenty nine presented with bilateral and three with unilateral disease. A history of consanguinity among the parents was present in 22 out of 32 patients. Sixty one eyes (32 patients) underwent surgery. Thirty eyes (16 patients) underwent trabeculectomy and the other 31 eyes (16 patients) underwent trabeculotomy. Only four patients had trabeculectomy in one eye and trabeculotomy in the fellow eye; otherwise either trabeculectomy or trabeculotomy was performed in both eyes except in unilateral cases. There were 19 eyes (10 in the trabeculectomy group and 9 in the trabeculotomy group) which presented with a corneal diameter greater than 14 mm. Ten patients (15 eyes trabeculectomy and 5 eyes trabeculotomy) presented with an initial IOP greater than 35 mmHg. Twenty eight patients (15 trabeculectomy and 13 trabeculotomy) presented with disease either at birth or soon after. The mean IOP by applanation tonometry was 35 mmHg, range 23–55 mmHg. The mean follow-up period was 11.2 months (range 3–30 months). Sixteen eyes (54%) were successfully treated in the trabeculectomy group compared with 21 eyes (67%) in the trabeculotomy group. This difference in success rate between the two groups was not statistically significant.

More serious complications such as loss of vitreous, endophthalmitis, and shallow anterior chamber occurred in the trabeculectomy group. Hyphaema was more common in the trabeculotomy group, but was benign and caused no additional problems (Table 1).

Discussion

It is our impression that congenital glaucoma is not uncommon in Saudi Arabia, while it is rare in the

Table 1 *Surgical complications*

Operation	Hyphaema	Shallow ant. chamber	Lens opacity	Posterior synechiae	Vitreous loss	Endophthalmitis
Trabeculectomy	1	1	1	2	3	1
Trabeculotomy	11	0	0	0	0	0

Western world. A history of consanguinity of the parents was present in 22 (68%) out of 32 patients in our study group, which suggests that the inherited form is more common in the Kingdom of Saudi Arabia owing to high consanguinity among Saudi couples than in the Western countries. Sixteen patients (30 eyes) underwent trabeculectomy and the other 16 patients (31 eyes) underwent trabeculotomy. Goniotomy and trabeculotomy have been shown to have a high success rate (80–93%) for congenital glaucoma in the Western world.^{7,9} However, our success rate with trabeculotomy was only 67% which is comparable to the success rate obtained by Kazi *et al.* in a similar group of patients treated at King Khaled Eye Specialist Hospital, Saudi Arabia.³ It appears that congenital glaucoma in Saudi Arabia does not respond so well to trabeculotomy as in the Western world. We share the belief of Kazi *et al.* that the main causes of failure from the trabeculotomy procedure in this Kingdom are: usually late presentation of the patient, cases being present at birth, more inherited cases, and more severe cases with larger corneal diameters, cloudy corneas, and high initial IOP at the time of presentation.³

Trabeculectomy for congenital glaucoma has not become popular owing to its variable success rate and higher complication rate. There are several reasons for this. They include anatomical factors such as enlargement, stretching, and thinning of the coats of the eye; deep anterior chambers with subluxated lenses; limbal ectasias and staphylomas; late fibrosis of the iris root and trabecular meshwork; late disappearance of Schlemm's canal and increased thickness of infantile and juvenile Tenon's capsule,^{10,18} complexity of associated pathology, management factors, and the number of previous operations.

Our success rate of 54% in the trabeculectomy group compares with a 50% success rate of Beauchamp and Parks,¹⁰ but it should be noted that their cut-off level was 24 mmHg, while ours was 16 mmHg. If a similar cut-off level is chosen, then our success rate goes up close to 60%. Mehta *et al.*¹¹ reported a 66.7% success rate in congenital glaucoma with trabeculectomy, but they studied only three patients. Similarly, Joesph and Livingston¹² reported a 48% absolute success without medical treatment and 28% partial success with medical treatment together with trabeculectomy in a study of 50 cases of congenital glaucoma with cut-off level for the IOP of 20 mmHg. Luntz¹³ reported a higher success rate of 95% with trabeculectomy, but most of his patients were older children and therefore not directly comparable with our patients. Werther¹⁴ reported a 90% success rate with trabeculectomy, but his follow-up period was very short and again was limited to a

small number of patients. Generous excision of Tenon's capsule, and partial thickness scleral flap dissection well beyond the limbus into the clear cornea, as recommended by Werther,¹⁴ may have contributed to our reasonable success rate in trabeculectomy. We are inclined to share the belief of Werther¹⁴ that increased thickness of Tenon's capsule and the subsequent scarring by it contributes to the failure of the filtering procedure in children.

CONCLUSION

The success rate of trabeculectomy and trabeculotomy procedures are very close in this study, but we still recommend trabeculotomy as an initial primary procedure because trabeculectomy carries a higher rate of complications. However, trabeculectomy may be an acceptable alternative when microsurgical facilities and specially trained surgeons are not available, as is the case in many developing countries.

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Prevention of the immediate intraocular pressure rise following argon laser trabeculoplasty

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SUMMARY A prospective, randomised double-masked study was undertaken to compare the effect of pretreatment with acetazolamide or placebo on the immediate intraocular pressure (IOP) rise following argon laser trabeculoplasty. One hundred eyes (100 patients) underwent 180° of laser treatment with a mean of 59 spots of 50 µm size and 800 to 1000 mW power. The IOP was measured during the first three hours after laser treatment, at 24 hours, and at two months. Forty-six patients (92%) in the placebo group had an immediate rise of IOP. The mean rise (SD) for these patients was 8.6 (7.1) mmHg. Fifteen patients (30%) in this group had an IOP rise of greater than 10 mmHg. Nine patients (18%) receiving acetazolamide had an immediate rise of IOP. The mean rise for these patients was 4.3 (3.1) mmHg, and no patient had an increase in IOP of greater than 8 mmHg. Acetazolamide appears to be effective in preventing a critical IOP rise after argon laser trabeculoplasty ($p < 0.0001$).

Argon laser trabeculoplasty has gained widespread acceptance as a valuable tool for the control of glaucoma. Its efficacy in the short term has been established,^{1,2} and recent reports are encouraging with regard to long term control.³⁻⁷ Its mode of action has not been clearly elucidated, though an increase in outflow facility has been demonstrated.^{1,8-11} A variety of complications of laser trabeculoplasty have been reported,¹²⁻¹⁶ the most serious being an immediate rise in intraocular pressure. Eyes already severely compromised by chronically raised intraocular pressure are susceptible to further damage from acute pressure elevations which may lead to field loss or loss of central vision.^{1,12-14,15,17}

It has been suggested that the extent of trabecular meshwork treated, as well as the number of burns, their energy, and placement, have a bearing on the degree of the pressure rise; though attention to these details may reduce the incidence of raised pressure, they do not eradicate it.¹⁶⁻²⁰ Several forms of pretreatment, including topical 4% pilocarpine,²¹ ALO 2145 (para-aminoclonidine),^{22,23} oral glycerin,²⁴ and oral acetazolamide,²⁵ have been reported to reduce

the frequency and severity of the pressure rise, while pretreatment with topical corticosteroid,²⁶ indomethacin,²⁷⁻³⁰ and flurbiprofen^{30,31} had no statistically significant effect.

We performed a prospective, randomised, double-masked study to evaluate the effectiveness of oral acetazolamide in preventing this pressure rise. A significant rise of IOP after argon laser trabeculoplasty is usually apparent by two hours, peaking between two and three hours and then declining; rarely a rise is first detected beyond this time.^{17,32-34} Oral acetazolamide reaches a peak plasma concentration one hour after administration of the drug (Fig. 1), the greatest fall in IOP occurs after two hours (Fig. 2) and declines only slightly up to six hours.^{35,36} Administration of acetazolamide one hour before argon laser trabeculoplasty should produce maximum IOP reduction to coincide with the period of potential maximum IOP elevation.

Patients and methods

In this controlled study all patients were white, aged 65 or over, and had uncontrolled open-angle glaucoma as defined by an IOP greater than 21 mmHg and progressive visual field loss. All were on the maximum tolerated topical therapy and none were

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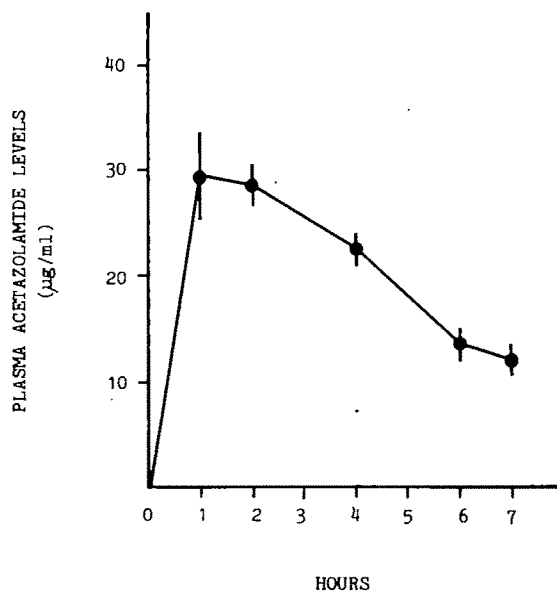


Fig. 1 Average plasma concentration (with SE) following oral administration of acetazolamide 500 mg in ocular hypertensive patients. Modified with permission from Friedland BR *et al.*³⁶

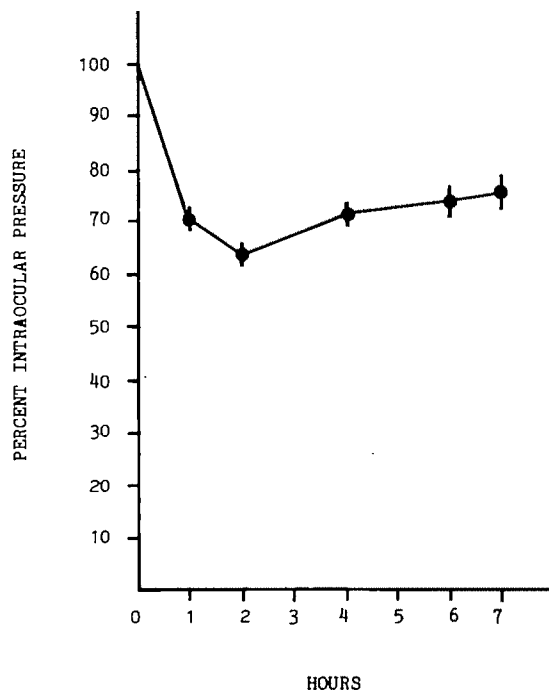


Fig. 2 Percentage (SE) of initial IOP following oral administration of acetazolamide 500 mg. Modified with permission from Friedland BR *et al.*³⁶

receiving acetazolamide, which in our experience is poorly tolerated in this age group. One eye of each patient was included in the study. None had previously undergone laser trabeculoplasty. If bilateral treatment was required, the eye treated first was included. Informed consent was obtained from all patients.

Before each treatment the patients underwent ophthalmic assessment of both eyes, which included best corrected Snellen visual acuity, slit-lamp examination of the anterior segment, and applanation tonometry. The patient was then randomly selected to receive either two 250 mg tablets of acetazolamide (group 1) or two placebo tablets (group 2). The medication selected was masked to both the patient and the physician. Acetazolamide or placebo were given orally, and one hour later the IOP was measured again immediately before argon laser trabeculoplasty. Topical anaesthesia was given with 0.4% oxybuprocaine. An antireflective Goldmann three-mirror contact lens was used to view the trabecular meshwork. A mean of 59 (SD 4.4) laser burns of 800 to 1000 mW power, 50 µm spot size, and 0.1 second duration were applied to the anterior trabecular meshwork. The burns were applied evenly over 180°, and the power was titrated to achieve blanching of the meshwork with occasional bubble formation. Blue-green argon laser light was used for all treatments and was delivered by a Coherent model 900 laser. The power output of the laser was measured at the start of the study and found to be 95% of the laser meter reading. All the laser treatments were applied by one of the authors (TM) and all examinations were conducted by the other (DE).

After laser treatment the IOP in both eyes and the degree of anterior segment inflammation in the treated eye were determined at 30 minutes, one hour, two hours, three hours, and 24 hours by the classification of Kimura *et al.*³⁷ Excessive intraocular pressure elevation was treated with 500 mg of intravenous acetazolamide and the patient monitored until the IOP had returned to baseline levels. An excessive IOP rise was defined as an increase of more than 30% or 10 mmHg above pretreatment levels provided the peak IOP was greater than 30 mmHg, after Krupin *et al.*³² Following laser trabeculoplasty the patients continued all their initial antiglaucomatous treatment with additional prednisolone 0.5% eye drops four times a day for three days. A further IOP check was made at two months.

Statistical data are reported as mean and SD, and were analysed by Student's *t* test, Fisher's exact test, Spearman's rank correlation coefficient, and multivariate regression analysis where appropriate. Values of *p* less than 0.05 were considered significant.

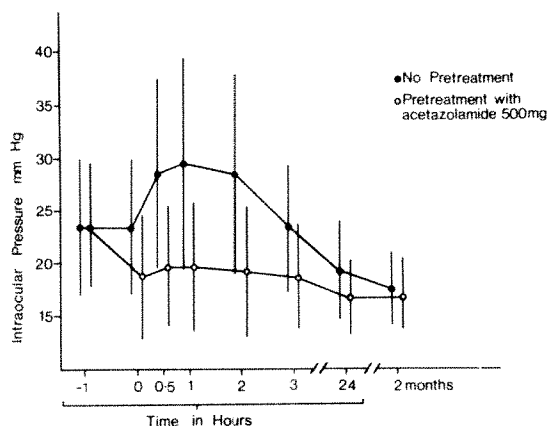


Fig. 3 Mean intraocular pressure (SD) before and after argon laser trabeculoplasty in patients receiving either acetazolamide (group 1) or placebo (group 2) pretreatment.

Results

One hundred eyes of 100 patients were treated. The mean age of group 1 was 74.0 years (SD 6.0) and of group 2 was 74.6 years (SD 5.9). The sex ratios were 27 female and 23 male in group 1, and 26 female and 24 male in group 2. None of the patients had secondary glaucoma or chronic narrow-angle glaucoma. Six patients in group 1 and seven in group 2 had pseudoexfoliative glaucoma; the remaining patients had chronic open-angle glaucoma. The mean pretreatment IOP in group 1 was 23.6 (6.1) mmHg and in group 2 23.7 (6.5) mmHg. There was

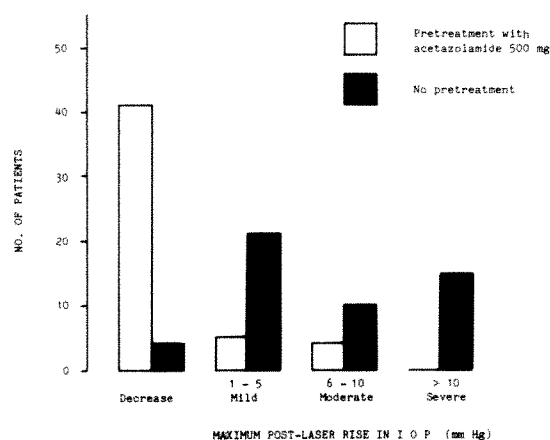


Fig. 4 Maximum intraocular pressure change following argon laser trabeculoplasty in patients receiving either acetazolamide (group 1) or placebo (group 2) pretreatment. Distribution is significantly different ($p < 0.0001$).

Table 1 Time elapsed from laser trabeculoplasty at which maximum IOP rise occurred

Time (hours)	0.5	1	2	3	24	Total
Number of patients						
Group 1 (acetazolamide)	2	3	3	1	0	9
Group 2 (placebo)	13	19	13	0	1	46

no significant difference between the mean pretreatment IOPs of the two groups ($p > 0.3$). Two patients in each group had a pretreatment IOP greater than 35 mmHg. The mean (with SD) IOPs before and after laser treatment at each examination time are presented in Fig. 3. The mean pressures were significantly lower in the acetazolamide pretreated patients (group 1) from time zero to 24 hours ($p < 0.001$ at time zero, 30 minutes, one, two, and three hours, and $p < 0.01$ at 24 hours). There was no significant difference at two months ($p > 0.3$).

The numbers of patients in each group showing either a decrease or a mild, moderate, or severe increase in postlaser IOP are represented in Fig. 4, and the time at which the maximum IOP increase occurred is shown in Table 1. One patient with pseudoexfoliative glaucoma in group 2 experienced a rise of 5 mmHg (21%) over the pretreatment IOP at 24 hours; in all other cases the maximum increase had occurred by three hours. Nine patients (18%) in group 1 had a postlaser rise in IOP ranging from 1 to 8 mmHg, mean 4.3 (SD 3.1) mmHg. The mean rise for the group as a whole was 0.8 (2.1) mmHg. None of the rises in pressure were significant as defined by Krupin *et al.*¹² In group 2 46 patients (92%) had a postlaser rise in pressure, the range being 1 to 25 mmHg, mean 8.6 (7.1) mmHg. The mean rise for the group as a whole was 7.8 (7.2) mmHg. Fifteen patients (30%) had a significant increase in IOP as defined by Krupin *et al.*¹² In these patients intravenous acetazolamide was administered and produced satisfactory reduction in IOP in all cases.

There was a highly significant increased risk of an immediate postlaser IOP rise in group 2 compared with group 1 ($p < 0.0001$, Fisher's exact test). The amplitude of the rise was also significantly higher in group 2 ($p < 0.01$). We found no significant difference in the risk of a critical postlaser pressure rise between patients with pseudoexfoliation and those without ($p > 0.3$, Fisher's exact test). There was no significant difference in the pressure drop at two months between the two groups; the mean pressure drop for group 1 was 6.8 (4.9) mmHg and for group 2 6.2 (5.5) mmHg. An excessive postlaser rise in intraocular pressure did not significantly compromise the result-

ing IOP at two months (Spearman's rank correlation coefficient).

Stepwise multivariate regression analysis showed there was no correlation between the postlaser pressure rise and age, sex, pretreatment IOP, previous antiglaucoma medication, number of burns administered, or postlaser inflammatory score. It also established that the only variable significantly to affect the pressure drop at two months was the initial IOP: the greater the initial IOP the greater the fall in IOP. This concurs with the findings of other authors.^{1 15 16}

Discussion

The risk of an intraocular pressure rise immediately after laser trabeculoplasty has been widely reported and is confirmed by our study. The cause of the rise has not been elucidated. It has been suggested that prostaglandins released as part of the inflammatory response following laser trabeculoplasty may be the cause, as certain prostaglandins applied topically have been shown to increase the IOP.⁸ However, prostaglandin inhibitors have shown no beneficial effect.²⁶⁻³¹ Inflammatory debris silting up the trabecular meshwork has been implicated, but our study and others have found no correlation between inflammatory scores and postlaser IOP rises.^{27 30 31} It seems more probable that localised structural changes and oedema in the trabecular meshwork resulting from the laser burn temporarily reduce aqueous outflow, leading to a rise in IOP. This may be aggravated by an exudative response of the damaged trabecular cells producing a transient pseudomembrane,³⁹ further blocking egression of aqueous.

All investigators agree that an acute increase in intraocular pressure is deleterious and can lead to further loss of visual field or loss of central vision in a glaucomatous eye. Although Hoskins *et al.*¹³ did not find pretreatment with acetazolamide effective, we agree with Brooks *et al.*²⁵ that acetazolamide confers a high degree of safety. Our results of a large prospective, randomised series showed that pretreatment with 500 mg of oral acetazolamide is effective in decreasing both the frequency and the magnitude of the immediate IOP rise after argon laser trabeculoplasty. Pretreatment with acetazolamide had no effect on the results of argon laser trabeculoplasty at two months. None of our patients reported side effects from acetazolamide beyond slight paraesthesiae and mild gastrointestinal disturbance.

This study shows that the safe and widely available drug acetazolamide is of major value in preventing an acute pressure rise in patients undergoing argon laser trabeculoplasty.

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Occurrence of malignant glaucoma after laser iridotomy

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SUMMARY A case is described of malignant glaucoma with extreme shallowing of the anterior chamber (AC) and an abnormally high intraocular pressure (IOP) following laser iridotomy for acute angle closure glaucoma. The episode followed the use of strong miotic (pilocarpine hydrochloride 4%) and was reversed by mydriatics including phenylephrine hydrochloride. Serial estimation of anterior chamber depth is important in the management of angle closure glaucoma.

Malignant glaucoma has been described as a condition in which, after operation for glaucoma, the anterior chamber (AC) becomes extremely shallow or flat and the intraocular pressure (IOP) abnormally high.¹⁻³ Cases have been reported after peripheral iridectomy^{4,5} and may even occur when strong miotics are used in the presence of a shallow anterior chamber without surgical operation.^{6,7} So far we

believe no case has been reported following laser iridotomy.

Case Report

A 73-year-old white Caucasian male was admitted to hospital on 5 March 1988 with a one-day history of a painful right eye. He was a smoker and alcoholic on methyl dopa (Aldomet) 250 mg three times a day and had extensive peripheral vascular disease, with a right above-knee amputation.

The visual acuities were R 6/36, L 6/18. The R pupil was semidilated and poorly reactive to light. There were 2+ cells in the right AC, and the IOPs by Goldmann applanation were R 56, L 18 mmHg. The irides were grey and normal. On gonioscopy the R angle was closed all around. The L angle was narrow with a small slit open all around. There was a R central retinal vein occlusion with macular oedema (Fig. 1). The optic cup disc ratio was 0.5 R and L.

On 8 March following treatment of the R eye, with pilocarpine hydrochloride 4% four times daily, timolol maleate (Timoptol) 0.25% twice daily, prednisolone acetate (Prednefrin forte) 1% four times daily, and acetazolamide (Diamox) 250 mg four times daily orally the R IOP was 16 and the L 12 mmHg. The corneal thickness was 0.56 mm and AC depth 1.3 mm R and L as measured with the Haag-Streit pachymeter. The R angle was open all round.

The patient underwent a YAG laser peripheral iridotomy of seven burns at 6.9 mJ in the R eye and 10 burns at 7.0 mJ in the L eye. In each eye a cloud of pigment was released into the AC with a gush of aqueous on complete penetration of the iris.

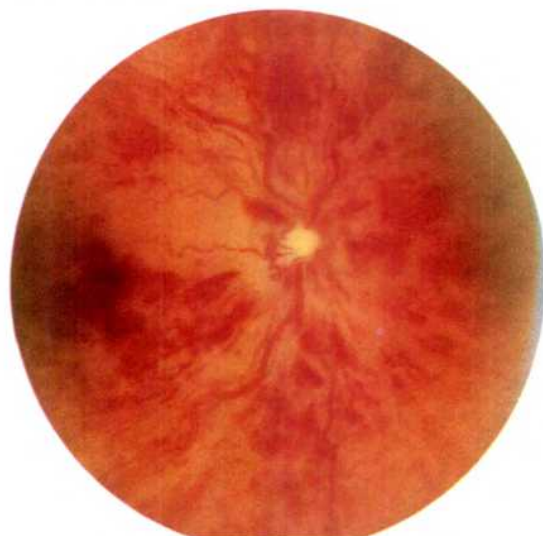


Fig. 1 Fundus appearance of right eye showing haemorrhagic central retinal vein occlusion. The cup-disc ratio is 0.5.

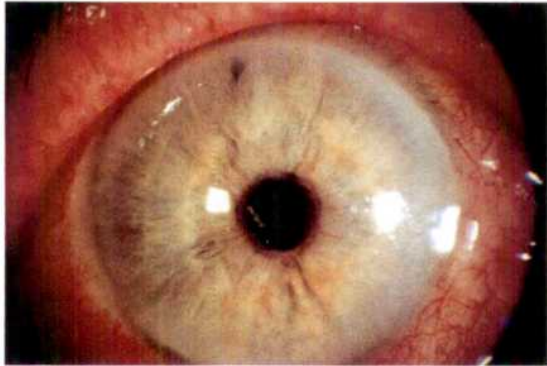


Fig. 2 Slit-lamp appearance of the affected right eye showing patent peripheral iridotomy and normal iris architecture.

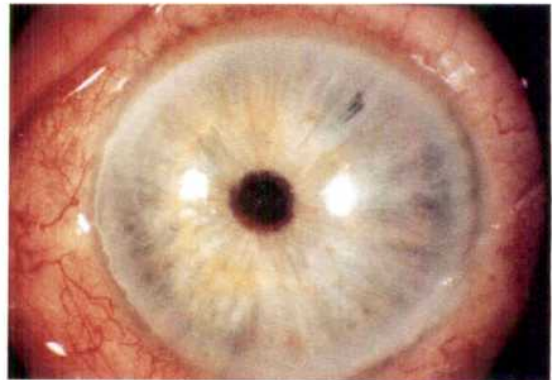


Fig. 3 Slit-lamp appearance of the fellow left eye showing patent peripheral iridotomy and normal iris architecture.

The initial iridotomy was enlarged somewhat in each case until the iridotomy was obviously patent on slit-lamp examination (Figs. 2, 3).

On 11 March the IOP was R 32, L 30 mmHg on only timolol maleate and fluorometholone (FML) 0.1% four times daily, and pilocarpine hydrochloride 4% four times daily was recommenced in each eye. On 13 March the IOP was R 46, L 18 mmHg, and the right AC depth was extremely shallow, being only 0.7 mm, while on the left it was 1.7 mm. The R angle was closed all round (Fig. 4). The L angle was open (Fig. 5). A provisional diagnosis of right malignant glaucoma was made, and acetazolamide 250 mg four times daily by mouth was started with homatropine hydrobromide (Homatropine) 5% and phenylephrine hydrochloride (Neosynephrine) 10%.

On 17 March the right AC had deepened to 1.5 mm, the L was 1.7 mm, and the IOP was R 21, L 15 mmHg. The R angle was now open (Fig. 6).

Panretinal photocoagulation was performed on the R eye in two sittings (422 and 622 spots of 200 μ m at 0.4–0.6 watt intensity and 0.1 second duration). On 25 March phenylephrine hydrobromide was stopped because of a local allergy. He was discharged from hospital on timolol maleate 0.25% twice daily and atropine sulphate 1% daily to the R eye and pilocarpine hydrochloride 4% four times daily to the L eye.

At follow-up on 12 April the IOP was R 55, L 17 mmHg. The R angle was closed above but open

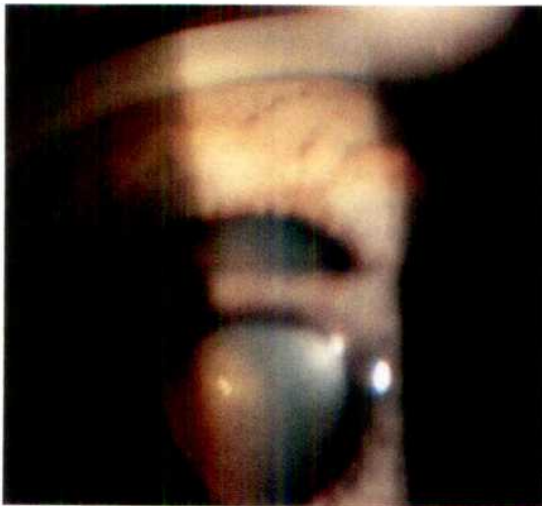


Fig. 4 Gonioscopic appearance of right eye showing the angle closed by iridocorneal apposition with moderate bowing of the iris.



Fig. 5 Gonioscopic appearance of left open angle with slight bowing of the iris and moderate trabecular pigmentation.

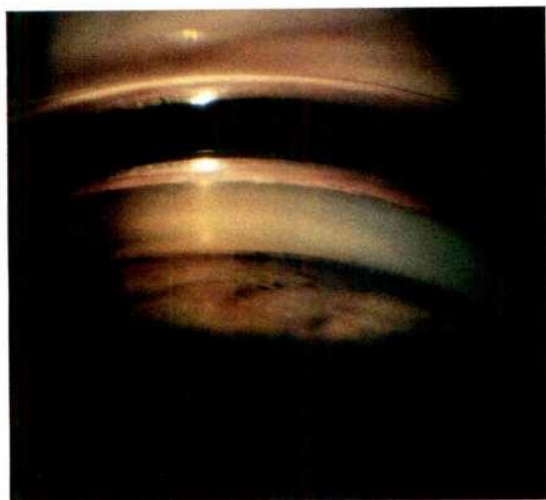


Fig. 6 Gonioscopic appearance of right angle below, now open, with marked pigmentation along the line of the canal of Schlemm.

below from 4 to 6 o'clock, with 80% peripheral anterior synechiae. The R AC depth was 1.6 mm. Atropine was stopped, and he was given timolol maleate 0.25% twice daily.

On 7 June 1988 he attended after having been off eyedrops for two weeks. The AC depth was R 1.6 mm, L 1.7 mm, the IOP was R 26, L 24 mmHg, and both angles were open. Timolol maleate 0.25% twice daily was started again but he was lost to follow-up.

Discussion

Shaffer discussed the possibility of ciliolenticular block initiated by the use of strong miotics in an unoperated eye causing malignant glaucoma when the ciliary body and the edge of the lens entrapped the aqueous flow, so that aqueous did not enter the AC, leading to extreme shallowing of the AC, angle closure, and malignant glaucoma.^{9,10}

Lowe¹¹ noted that following peripheral iridectomy for angle closure half to two thirds of these narrow angles may close with pupillary dilatation by mydriatics, adrenaline-like mydriatics being safer than tropine-like mydriatics.¹²⁻¹⁴

In the present case a high rise in IOP with extreme shallowing of the AC followed the use of pilocarpine hydrochloride 4% after a patent laser iridotomy had been performed, a finding consistent with Shaffer's observations.^{9,10} The AC deepened and the IOP fell to a normal level with phenylephrine hydrochloride 10% and homatropine hydrobromide 5%. However, when the phenylephrine hydrochloride was discontinued and the patient discharged on atropine

sulphate 1%, the angle closed once more, with an abnormally high rise in IOP, though the AC did not become shallow, which is consistent with Lowe's observations.¹¹⁻¹⁴

Thus, although the use of pilocarpine hydrochloride 4% caused extreme shallowing of the AC and a high rise in IOP, this was reversed by homatropine hydrobromide and phenylephrine hydrochloride, an adrenaline-like mydriatic. Dilatation with phenylephrine hydrochloride was probably crucial in breaking the ciliolenticular block, demonstrating the usefulness of this type of mydriatic after peripheral iridotomy in angle closure.

The late rise in IOP with angle closure but no shallowing of the AC following atropine sulphate demonstrates the tendency of strong tropine-like mydriatics to cause angle closure and a rise in IOP following iridotomy for angle closure.

The risk of some shallowing of the AC leading to angle closure glaucoma after central retinal vein occlusion is well known,¹⁵⁻¹⁷ but initially the AC depths were almost equal in this patient with central retinal vein occlusion, and the episode of a high rise in IOP with extreme shallowing of the AC preceded the use of panretinal photocoagulation.

This case shows that a condition consistent with malignant glaucoma may follow laser iridotomy for angle closure glaucoma, and it illustrates the previously described risks of both strong tropine-like mydriatics and strong miotics in such patients with very shallow ACs and an unstable lens iris diaphragm. It also emphasises the importance of serial estimation of anterior chamber depths in the management of difficult cases of angle closure glaucoma.

This work was carried out under Research Projects 101 and 126 of the Royal Victorian Eye and Ear Hospital, East Melbourne, Victoria 3002, Australia.

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Decreased formation of aqueous humour in insulin-dependent diabetic patients

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SUMMARY The rate of aqueous humour formation was measured by fluorophotometry in 34 insulin-dependent diabetic patients and 12 non-diabetic controls to determine whether or not aqueous flow in diabetics differed from that of normal controls, and whether or not aqueous flow among diabetics was correlated with the stage of retinopathy. Diabetic patients were divided into three groups based on the degree of retinopathy; group I without retinopathy, group II with minimal to moderate non-proliferative retinopathy, and group III with proliferative retinopathy. Aqueous flow (mean, SD) in diabetic patients was: 1.55 (0.32) $\mu\text{l}/\text{min}$ in group I, 1.51 (0.47) $\mu\text{l}/\text{min}$ in group II, and 1.26 (0.39) $\mu\text{l}/\text{min}$ in group III. No statistically significant difference was found among these three diabetic groups. Aqueous flow in the non-diabetic controls was 2.18 (0.40) $\mu\text{l}/\text{min}$, and this was statistically significantly greater than in each of the diabetic groups. Intraocular pressure, age, duration of diabetes, haemoglobin A_{1C}, and blood glucose levels had no significant effect on aqueous flow in diabetic patients.

Several studies have found that diabetic patients without retinopathy have higher intraocular pressure (IOP) than those with retinopathy, in particular, proliferative retinopathy.¹⁻⁴ We believe there has been no report on the rate of aqueous formation in diabetic patients. The purpose of this study was to investigate whether or not the degree of diabetic retinopathy is associated with an altered rate of aqueous humour formation. We also looked at possible effects of other variables on aqueous flow in diabetic patients such as IOP, age, duration of diabetes, haemoglobin A_{1C}, and blood glucose levels.

Material and methods

Thirty-four insulin-dependent diabetic patients without rubeosis iridis were included in this study. Their mean age (SD) was 36.6 (11.3) years. The duration of diabetes ranged from eight to 33 years, mean 17.3 (6.3) years. Twelve normal controls with mean age 33.1 (5.5) years were also studied.

On the morning of the fluorophotometric study to determine aqueous flow one drop of fluorescein

solution (Fluress) was applied to each eye every five minutes for a total of 10 applications. Four and a half hours after the last drop of fluorescein was applied, fluorophotometric measurements with a Fluorotron Master (Coherent; Palo Alto, CA) of the fluorescein concentrations in the cornea and anterior chamber were begun and were repeated at 30-minute intervals over two and a half hours. After the last fluorophotometric measurement the IOP was measured with a pneumatonometer (Alcon; Fort Worth, TX). Aqueous flow was calculated by the Jones and Maurice method modified by Yablonski and associates.⁵

In diabetic patients venous blood was drawn for the determination of haemoglobin A_{1C} (n=31). Blood glucose levels were determined by averaging values of the venous blood obtained at the completion of the fluorescein eye drops and at each fluorophotometric measurement (n=26).

The pupils of the diabetic patients were dilated after fluorophotometry and the fundi were examined by ophthalmoscope by one of the authors (MEY). Multiple field retinal photographs were also obtained in 20 of the diabetic patients and classified in a masked fashion by MEY. Patients were classified according to the degree of retinopathy: group I with no retinopathy, group II with non-proliferative

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Table 1 Aqueous flow and variables in diabetic patients

	No. of patients			Aqueous flow*	
	Total Group			(µl/min)	
	I	II	III		
IOP (mm Hg)					
<15	20	6	10	4	1.44 (0.43)
≥15	14	3	8	3	1.50 (0.50)
Age (years)					
19-30	11	3	4	4	1.30 (0.40)
31-45	16	4	10	2	1.60 (0.47)
46-65	7	2	4	1	1.44 (0.24)
Duration of diabetes (years)					
1-15	17	4	12	1	1.50 (0.45)
16-33	17	5	6	6	1.40 (0.39)
HbA _{1c} (%)					
<7.5	16	4	9	3	1.47 (0.49)
≥7.5	15	3	8	4	1.39 (0.36)
Average blood glucose (mg/dl)					
<160	10	1	7	2	1.63 (0.35)
≥160	16	6	7	3	1.52 (0.38)

*Values are means (SD).

retinopathy, and group III with proliferative retinopathy.

None of the patients or controls had been on beta blockers or carbonic anhydrase inhibitors either systemically or topically for at least four weeks before the study. None took any eye medications on the day of the study, and their insulin doses were given as usual.

Results

In no instance did the classification of photographs differ from that of the funduscopic examination. In 24 diabetic patients both eyes were classified as belonging to the same group. Eight patients had one eye in group I and the other eye in group II, and two patients had one eye in group II and the other in group III. Since no statistically significant difference was found in IOP and aqueous flow between the two eyes of these 10 patients whose classification fell into two groups, they were classified according to the worse eye. The numbers of patients in each group were, 9 in group I; 18 in group II; and 7 in group III. In all subjects the values of the IOP and aqueous flow of both eyes were averaged and treated as one eye.

The mean (SD) aqueous flow in normal controls was 2.18 (0.40) µl/min. In groups I, II, and III of the diabetic patients aqueous flow was 1.55 (0.32) µl/min, 1.51 (0.47) µl/min, and 1.26 (0.39) µl/min, respectively. All the three diabetic groups showed aqueous flow values statistically less than that in the control group ($p < 0.05$, Student's *t* test). Aqueous flow in each diabetic group, though having a trend of

decreasing rate with increasing severity of retinopathy, showed no statistically significant difference among groups ($p > 0.05$, analysis of variance).

IOP, age, duration of diabetes, haemoglobin A_{1c}, and blood glucose levels had no significant effect on aqueous flow ($p > 0.05$, Student's *t* test, Table 1). The IOP was found not to be related to the degree of retinopathy ($p > 0.05$, Fisher's exact test, Table 1).

Five patients in group III had previous panretinal photocoagulation (PRP) for proliferative retinopathy. Three patients received PRP in one eye and two in both eyes. Aqueous flow in eyes with PRP was 1.30 (0.49) µl/min compared with 1.21 (0.36) µl/min in eyes without PRP in group III. This difference was not statistically significant ($p > 0.05$, Student's *t* test).

Discussion

A statistically significant decrease in aqueous humour formation was found in diabetics, and this decrease was not significantly affected by the degree of retinopathy. Aqueous flow was also unrelated to the duration of diabetes, age of patients, haemoglobin A_{1c}, average blood glucose levels, and IOP. There was no significant difference in IOP between the diabetic groups with and without proliferative retinopathy. It has been suggested¹⁴ that a raised IOP may tend to protect against the onset and progression of retinopathy. However, Valone *et al.*⁶ studying eyes with initially non-proliferative retinopathy, found that eyes with a raised IOP progressed to proliferative retinopathy as frequently as eyes with a normal IOP.

Although the number of subjects in this study may not have been large enough to detect small differences, these findings suggest that the decrease in aqueous flow may be secondary to a fundamental alteration in the physiology of the diabetic eyes. Many possible explanations exist.

The formation of aqueous humour by the ciliary body is largely an active process, requiring energy. Therefore, ischaemia of the ciliary body might be expected to decrease aqueous flow. It seems likely that the diabetic eye suffers from ischaemia because of a variety of circulatory abnormalities in diabetics, including a generalised angiopathy,⁷ an increased blood viscosity,^{8,11} and impaired oxygen release by the red blood cells due to decreased 2,3-diphosphoglycerate (2,3-DPG) and increased glycosylated haemoglobin.¹² A generalised abnormality of transport processes¹³ in diabetes may affect the ciliary body as well. Na⁺-K⁺ ATPase is related to active secretion of aqueous humour in the ciliary body, and insulin has been shown to affect the activity of this enzyme.¹³ Generalised neuropathy is common in diabetics¹⁴ and it may also affect the

ciliary body, which is innervated by the sympathetic nervous system.¹⁵

A reduced rate of aqueous flow leads to decreased delivery of nutrients to and decreased removal of metabolic wastes from avascular tissues such as the lens and trabecular meshwork. Therefore the decreased flow of aqueous humour in the insulin-dependent diabetic eye may possibly be related in part to some common diabetic ocular sequelae such as the greater incidence of cataract¹⁶ and primary open-angle glaucoma.³ Furthermore, it might predispose to the development of rubeosis iridis by impeding the washout of vasoproliferative factors released by the retina.¹⁷

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Tonicity of human tear fluid sampled from the cul-de-sac

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SUMMARY A 'freezing point' depression technique was used to determine the osmolality of 384 samples of tear fluid originating from the middle of the lower tear prism and the lower cul-de-sac of one eye of each of 12 young adults. Tear fluid from the cul-de-sac (mean 341.0 mosm/kg) was found overall to be significantly hypertonic ($p < 0.0001$) relatively to fluid from the tear prism (mean 315.5 mosm/kg). However, the difference between the two sampling sites was highly variable between individuals, ranging from a maximum mean site difference of 64.5 mosm/kg for one of the six cul-de-sacs found to be significantly hypertonic, to a mean site difference of 25.0 mosm/kg for one of the two cul-de-sacs found to be significantly hypotonic. These results suggest that a unique localised tear environment exists inside the lower cul-de-sac, which has several clinical consequences—for example, for pharmaceutical absorption, ocular microbiology, and hydrophilic contact lens performance.

Temporal and spatial variations in the osmolality of human tear fluid have been observed across the ocular surface by sampling of tear fluid in amounts of approximately 0.2 μ l from the mid point of the lower tear prism^{1,2} and also from tear prism sites at other locations.³ While the surface tear fluid has been shown in these studies to be osmotically heterogeneous in the open-eye state, it is not clear to what degree and in which direction of magnitude the tear fluids within less exposed parts of the ocular adnexa (that is, within the cul-de-sacs) may vary from fluid at the surface of the eye.

The routes and rates by which tear fluids in the cul-de-sacs are turned over have received little experimental attention but must be assumed to be different and slower, respectively, than the normal flow of surface tear prisms owing to probable 'entrapment' of fluid inside the fornices. The purpose of the present study was to test for osmotic differences between tear fluids sampled from the lower tear prism, being the reference point from which most previous work has been performed, and the lower cul-de-sac, from which samples could also be taken without stimulation of reflex tearing.

Material and methods

Tear fluid osmolality determinations were made with a 'freezing point' osmometer capable of at least 1% accuracy with fluid samples of approximately 0.2 μ l.¹⁴ The experimental technique was based on the measurement of melting point of tear samples and its relationship to tear osmolality. A pilot study was first attempted by sampling with finely drawn microcapillary tubes the tear fluid at the middle of the lower tear prism and then from the lower cul-de-sac of the left eye of each of two young adults. While subject 2 was asymptomatic, subject 1 had occasional complaints of dry eye, though no ocular surface staining with rose Bengal was biomicroscopically noted (nor was staining noted on any subject).

Tear samples were each immediately loaded into oil and simultaneously processed with a standard calibration liquid,¹ a technique confirmed by Martin⁵ to give repeatable results realistic to the tonicity of human tear fluid.⁶ After analysis of the preliminary data indicated that an osmotic difference between the two sampling positions was probable, an expanded series of osmolality determinations was performed for the two sampling sites of each subject. A total of 184 osmolality determinations resulted from the processing of these initial samples.

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Ten additional asymptomatic young adult subjects were then added to the study, bringing the mean age of the 12 subjects in the whole study to 25.3 years (range 22 to 32 years). Each of the 10 additional subjects submitted 10 pairs of tear samples (10 samples from the lower tear prism and 10 samples from the cul-de-sac), every pair of samples consisting first of fluid taken from the lower tear prism and then also from the cul-de-sac. Sample pairs were taken at least 15 minutes apart, and osmolality determinations for both tear fluids of each pair of samples were made simultaneously with the standard calibration liquid.

Results

An analysis of variance⁷ performed unweighted with respect to the additional number of measurements recorded for subjects 1 and 2 ($F(1,360)=37.58$, $p<0.0001$) revealed that, for the population, the mean osmolality of tear fluid taken from the cul-de-sac (341.0 mosm/kg) was significantly higher than that taken from the lower tear prism (315.5 mosm/kg). The main effect of subject was significant ($F(11,360)=15.52$, $p<0.0001$), as was also the interaction between subject and sampling location ($F(11,360)=2.74$, $p<0.0021$).

The mean tear fluid osmolalities with standard deviations for the two sampling sites of each subject and of the population are shown in Table 1. Analyses of variance were computed from the data from each subject alone and from the population (as noted above); the corresponding critical statistics are shown in Table 1. Single asterisks have been placed

Table 1 Mean tear fluid osmolalities in mosm/kg (SD in parentheses) for samples taken from the lower tear prism and cul-de-sac of 12 subjects. *F* values and probability levels for the differences between site means of each subject, and of the population, are also shown

Subject	Mean lower prism	n	Mean cul-de-sac	n	<i>F</i> (df 1, df 2)	<i>p</i> Value
1	344.0 (61.7)	51	408.5 (57.6)	32	22.53 (1,81)	0.0001*
2	326.5 (50.3)	57	370.0 (65.4)	44	14.37 (1,99)	0.0003*
3	304.0 (13.1)	10	280.5 (14.8)	10	14.15 (1,18)	0.0014*
4	311.0 (19.7)	10	330.5 (24.3)	10	3.88 (1,18)	0.0643**
5	323.5 (42.8)	10	314.0 (36.5)	10	0.29 (1,18)	0.5999
6	327.0 (35.8)	10	302.0 (11.1)	10	4.46 (1,18)	0.0490*
7	293.0 (43.7)	10	337.5 (26.4)	10	7.59 (1,18)	0.0130*
8	277.0 (39.8)	10	299.0 (30.7)	10	1.91 (1,18)	0.1834
9	244.0 (56.0)	10	253.0 (49.9)	10	0.14 (1,18)	0.7088
10	297.0 (40.4)	10	303.0 (55.9)	10	0.08 (1,18)	0.7864
11	267.0 (51.7)	10	308.0 (52.9)	10	3.08 (1,18)	0.0964**
12	306.0 (16.8)	10	337.5 (21.6)	10	13.07 (1,18)	0.0020*
All	315.5 (54.6)	208	341.0 (66.1)	176	37.58 (1,360)	0.0001*

*Comparisons significant to at least the 0.05 level.

**Comparisons significant to at least the 0.10 level.

next to the statistics of those subjects for which the mean tear fluid osmolalities of the two sampling sites were found to be significantly different to at least the 0.05 level. Two asterisks have been placed next to those statistics indicating significance to at least the 0.10 level. The mean osmolalities for each subject are plotted in Fig. 1, and a linear correlation between the mean cul-de-sac and tear prism values of the 12 subjects shown in Table 1 (12 pairs of mean data points) resulted in a correlation coefficient of +0.72.

Discussion

Osmotic variations of human tear fluid have been reported between several collection sites at the tear fluid prisms surrounding the exposed ocular surface.³ Tear fluid at these sites may be vulnerable to environmental influences, such as ambient humidity, temperature, and flow of air across the surface of the eye, in addition to the effects of pollutants and reflex tearing. Less vulnerable to outside influences, perhaps, might be tear fluid within the cul-de-sac, where the immediate environment may be more stable as in a more 'closed' system.

In comparison with the osmolality of tear fluid sampled from the lower tear prism, a standard site from which tear osmolality determinations have been routinely made, the fluid from the lower cul-de-sac was generally hypertonic over the population of subjects shown in Table 1 and Fig. 1. Tear fluid from the lower cul-de-sac was 8% (25.5 mosm/kg) more hypertonic, on average, than that of the lower tear prism established in rooms averaging 23°C and 43% relative humidity. This site difference should be considered on the conservative side, because on opening of the lower cul-de-sac for sampling some mixture from the lower tear prism could have occurred, thus possibly reducing the average tonicity of fluid sampled from the cul-de-sac.

The subject means for the two collection sites were positively correlated (Fig. 1), with a correlation coefficient of +0.72, and statistically significant differences between the mean tonicities of the two collection sites were found for 8 of the 12 subjects. The site difference was greatest for subject 1 (the 'dry eye' patient who also had the highest tear fluid tonicities), for whom the cul-de-sac fluid was 408.5 mosm/kg, or 19% (64.5 mosm/kg) more hypertonic than fluid from the lower tear prism. Relatively hypertonic cul-de-sac fluid was statistically supportable for six of the subjects (subjects 1, 2, 4, 7, 11, and 12), the cul-de-sac osmolality for these subjects ranging as low as 308.0 mosm/kg for subject 11. The minimum statistically significant site difference was 6% (19.5 mosm/kg) in the case of subject 4, for which

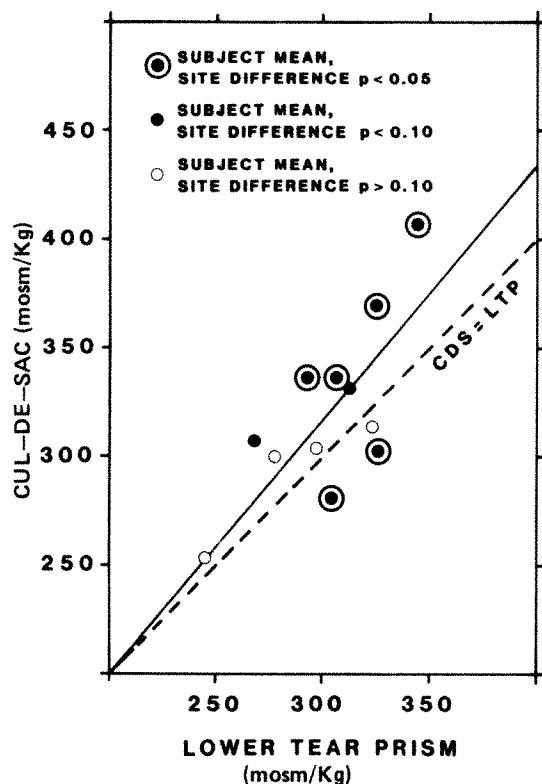


Fig. 1 The mean tear fluid osmolalities for the lower cul-de-sac (CDS) and lower tear prism (LTP) of each of the 12 subjects have been plotted. An open circle represents a site comparison in which cul-de-sac and lower tear prism mean values were not significantly different. A filled circle represents a site comparison significant to at least the 0.10 level, while a filled circle surrounded by an annulus represents a site difference significant to at least the 0.05 level. The dashed line indicates where osmolalities of the two sites would be equal ($CDS=LTP$), produced for comparison with the actual mean data points and the solid linear regression line for those points, which had a correlation coefficient of +0.72.

the cul-de-sac fluid was more hypertonic than the tear prism average.

A reversed relationship was found for two subjects, in that hypotonicity of the cul-de-sac fluid was statistically supportable relative to tear fluid of the lower tear prism. The cul-de-sac fluid was 8% hypotonic for subjects 3 and 6 (site differences of 23.5 and 25.0 mosm/kg, respectively, in Table 1). Site differences were not statistically significant for subjects 5, 8, 9, and 10.

Cul-de-sac tear fluid therefore has a unique osmotic environment, tending to hypertonicity in most cases relative to the tear fluid tonicity of the lower tear prism. One might have expected, how-

ever, a general hypotonicity due to reduced evaporation of cul-de-sac fluid relative to tear prism fluid exposed to air, as did in fact occur for subjects 3 and 6. This hypothesis has been offered earlier for another 'closed' tear environment, that being the hypotonic shift of tear prism fluid found after sleep.⁸

More likely for the six subjects with hypertonic cul-de-sac fluids, however, are the effects of a possible reduction of aqueous tear circulation within the cul-de-sac area in comparison with the ocular surface. Accounts of tear fluid elimination⁹⁻¹¹ are not necessarily inclusive of fluids within the cul-de-sacs, and the efficiency of the elimination routes may vary between individuals. In addition, basic and reflex aqueous tear fluids primarily originate from structures of the upper eyelid and are possibly less prone to replenish the compartment of the lower cul-de-sac. It is therefore plausible that tear fluid within the lower cul-de-sac is less stirred than fluid from the ocular surface, with higher accumulations of ionic and other small-particle by-products from enzymatic breakdown of mucous strands^{12,13} and from the surrounding epithelial cell layers. Even for the four subjects not showing statistically significant site differences the competing effects of stagnation and reduced evaporation on tonicity within the cul-de-sac may have offsetting each other.

The presence of unique tear fluid 'compartments' within the lower cul-de-sac of individuals raises many questions related to future clinical studies. Could these tear compartments be more reliable indicators of incipient dry eye, being generally more hypertonic and perhaps less alterable by outside elements, than their ocular surface counterparts? Are not epithelial lesions in dry eye the cause of heightened tear osmolality (and not vice versa), given that human epithelial cells in the cul-de-sac seem to withstand a much higher tear fluid osmolality in some subjects than previously thought? Could disturbances of the cul-de-sac fluid have more effect on the stability of the ocular and palpebral surfaces during contact lens wear or on pathological states than previously recognised, since this fluid interacts with a more expanded and vascularised tissue than does the precorneal tear film? In addition, tear fluid osmolality may indicate the effectiveness of tear elimination in the lower cul-de-sac, and it may influence microbiological distributions around the eye as well as the hydration, retention, and drug delivery characteristics of various types of ocular inserts.

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Histopathological evaluation of rotation sutures for involutional entropion*

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SUMMARY Rotation sutures are a popular method of temporarily correcting involutional entropion. The permanence of the procedure depends on a fibrotic scar along the suture tracks. Sutures which create generous scars would probably produce the most satisfactory results. In this study 4–0 chromic gut, nylon, and silk sutures were evaluated in rabbit lower eyelids for their ability to create histologically demonstrable fibrous tracks. All three sutures incited inflammatory cells and fibroblastic activity with collagen formation at two and four weeks. Residual scar tracks were observed at six weeks (two weeks after suture removal) also. Human specimens showed similar types of scar formation from the sutures. It was apparent that all three sutures create fibrotic scars along their tracks sufficient to correct, at least temporarily, involutional entropion.

Involutional entropion has been attributed to laxity of the lower eyelid retractors, horizontal laxity of the lower eyelid or enophthalmos, and overriding mobile preseptal orbicularis muscle.^{1–3} Rotation sutures are a popular method of dealing quickly and simply with involutional entropion.^{4–11}

Variations of these techniques^{7–10} provide ways of dealing with two of the three generally proposed mechanisms for involutional entropion. The three horizontal mattress sutures are believed to create scar tracks which fix the overriding preseptal orbicularis muscle and reinforce the attachments of the lower eyelid retractors to the inferior tarsus. As a result the rotation suture repair of entropion is moderately successful, especially when considered as a temporary measure. Its limitations are probably related to the persistence of lower eyelid horizontal laxity and a weak suture track running from the retractors through the orbicularis to the skin. Chromic gut^{9–11} and silk^{7–10} sutures have been described in these techniques.

No studies have been previously performed to determine which sutures create adequate fibrotic scar

tracks and so probably the most satisfactory results. We have studied this question by examining reactions to non-absorbable silk, non-absorbable monofilament nylon, and absorbable chromic gut sutures in rabbit and human specimens.

Materials and methods

Pigmented rabbits were used for the preliminary part of this study. 4–0 Nylon, chromic, and silk sutures were placed in the lower eyelids of the pigmented rabbit in the manner of Feldstein.¹⁰ The sutures were tied under minimal tension so as to not create an irritating ectropion. They were left in place for two and four weeks. In addition the sutures were removed at four weeks in another specimen and the suture tracks allowed to heal for an additional two weeks. At the end of this time the tissue was examined histopathologically. The tissue was stained with haematoxylin and eosin and with a trichrome stain.

For the second portion of the study specimens of human tissue were examined. Rotation sutures were used for temporary relief in three patients with involutional entropion and horizontal laxity. The sutures were placed in horizontal mattress fashion deep into the fornix in an attempt to include the lower eyelid retractor attachments. They were then brought superiorly and anteriorly to a level just below the lashes. The double arms were placed approximately

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3 mm apart and tied on the skin under sufficient tension to create a mild ectropion. Three sutures were placed in each lower eyelid. The sutures were left in place for two weeks while the patients awaited a more definitive Quickert procedure^{2,3,12} with horizontal shortening. The horizontal shortening was performed in the segment of the eyelid which contained the lateral rotation suture. The inferior portion of the suture in the fornix was not included in the specimen. These segments were submitted for histopathological examination. The findings in these specimens are discussed below. Silk, chromic, and nylon sutures were again used.

Results

Each specimen was orientated with the anterior part of the lower eyelid to the left, posterior to the right, and superior and inferior aspects of the lid correspondingly.

RABBIT SPECIMENS

Two weeks after placement all three sutures (silk, chromic, and nylon) had created fibrous tracks coursing through orbicularis muscle from inferior posterior to superior anterior (Fig. 1 left). These suture tracks had active fibroblastic proliferation and collagen deposition. Lymphocytic infiltrates were noted as well (Fig. 1, right, Figs. 2, 3).

At four weeks the reactions to all three sutures were not significantly different from that seen at the two-week interval, though a somewhat more vigorous fibroblastic response with denser, more regular collagen formation was apparent. Epithelial cell ingrowth along the silk suture track was noted.

The residual collagen scar track could be identified in the six-week specimens (two weeks after suture removal) for all three sutures (Figs. 4-6). Areas of epithelial ingrowth were noted in the silk and nylon specimens (Figs. 4, 5). Trichrome staining of these

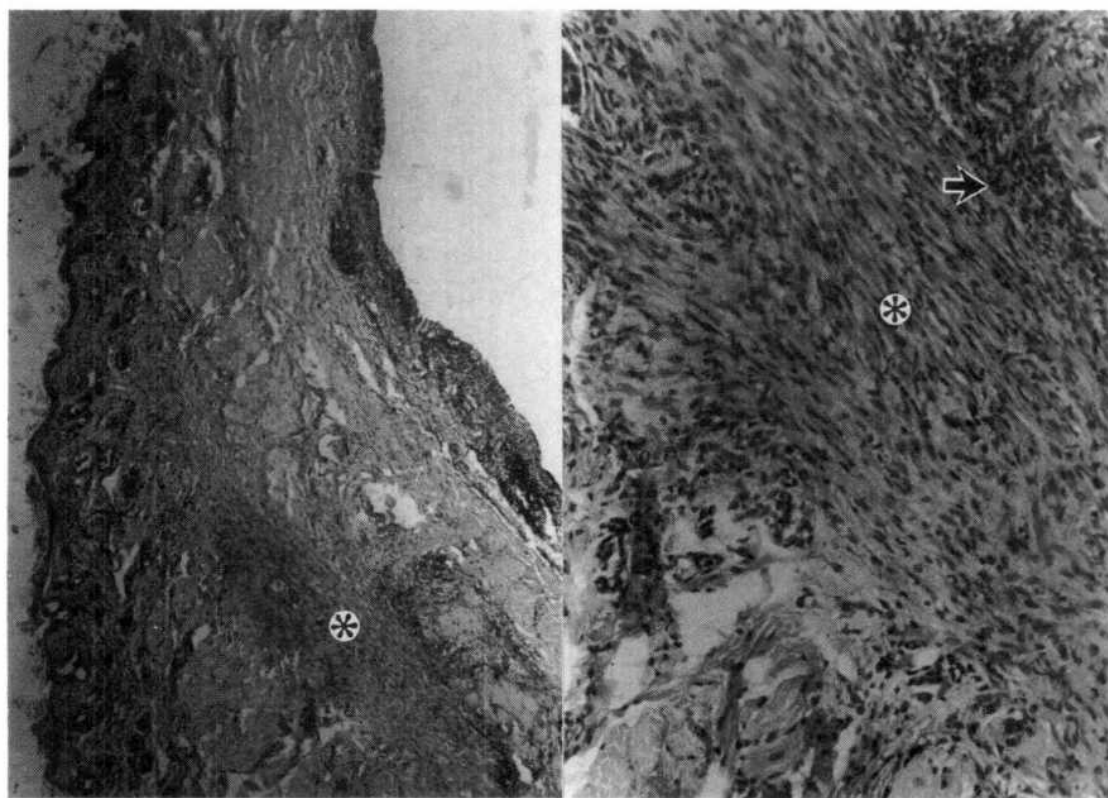


Fig. 1 Silk suture in rabbit for two weeks. Left: Suture track of active fibroblasts and collagen coursing through orbicularis muscle from inferior posterior to superior anterior eyelid (asterisk). (H and E, $\times 8$.) Right: Higher power view more clearly demonstrates the fibroblastic activity with collagen formation (asterisk). Some round chronic inflammatory cells are also seen (arrow). (H and E, $\times 33$.)

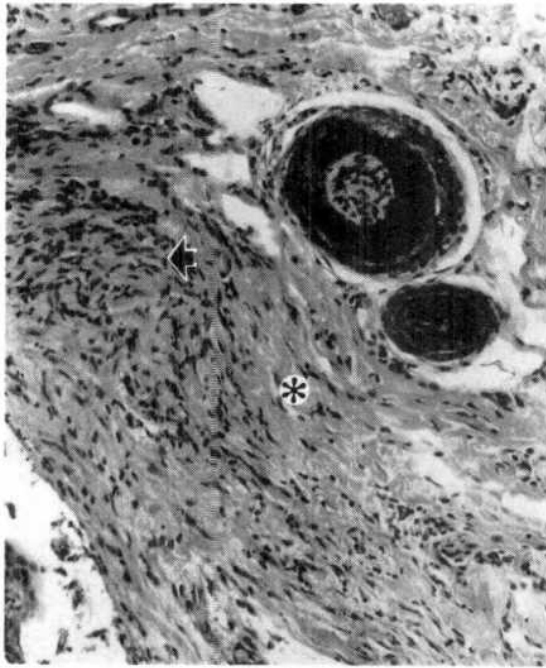


Fig. 2 Nylon suture in rabbit for two weeks. The suture track is composed of proliferating fibroblasts and collagen (asterisk) with chronic inflammatory cells (arrow). (H and E, $\times 32$.)

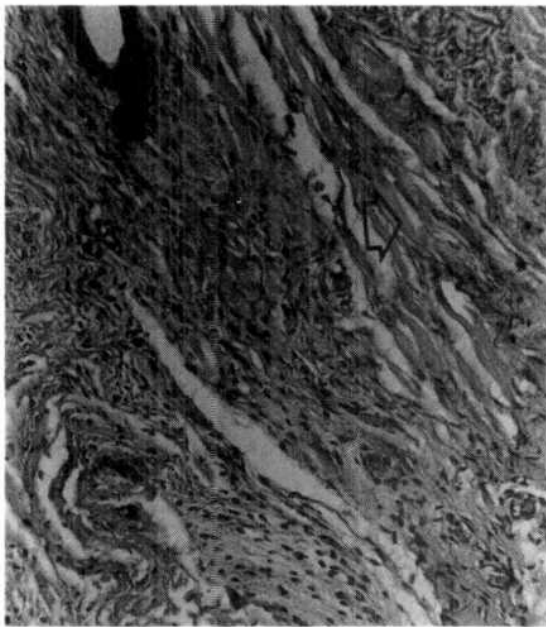


Fig. 4 Silk suture in rabbit, six-week specimen. The suture track is identified by fibroblasts and collagen (asterisk), atrophic orbicularis muscle fibres (hollow arrow), and epithelial cell ingrowth (solid arrow). (H and E, $\times 32$.)

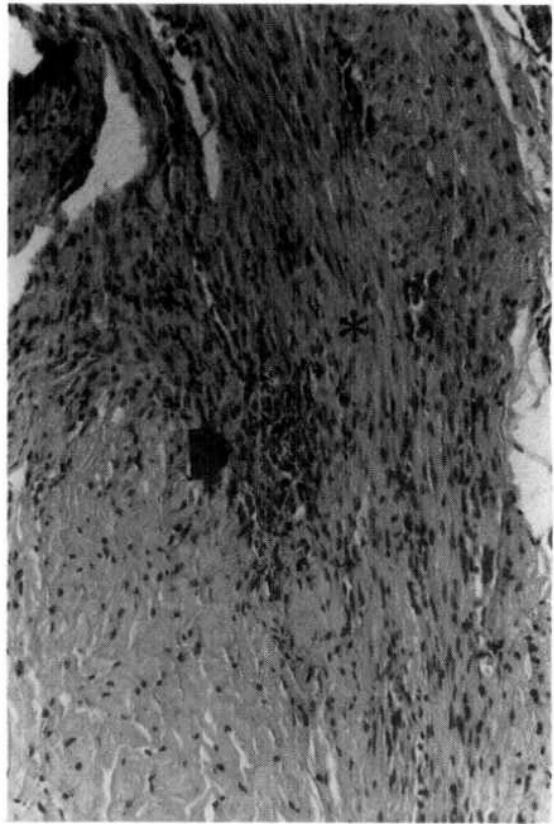


Fig. 3 Chromic gut suture in rabbit for two weeks. Fibroblastic proliferation and collagen formation are identifiable (asterisk) in the suture track. Inflammatory cells are noted (arrow). (H and E, $\times 32$.)

six-week specimens better showed the substantial collagen present in the scar tracks.

HUMAN SPECIMENS

All human specimens were examined at two weeks. At this time the silk suture remnant was noted coursing through orbicularis muscle, surrounded by an intense epithelioid cell reaction (Fig. 7). The nylon suture specimen showed epithelial cell ingrowth along the suture with surrounding collagen formation. Chronic inflammatory cells were also seen (Fig. 8). The chromic gut suture track showed regular collagen formation by active fibroblasts along with chronic inflammatory cells (Fig. 9).

Discussion

Rotation sutures for entropion are best viewed as a temporary method for correction of the inturning

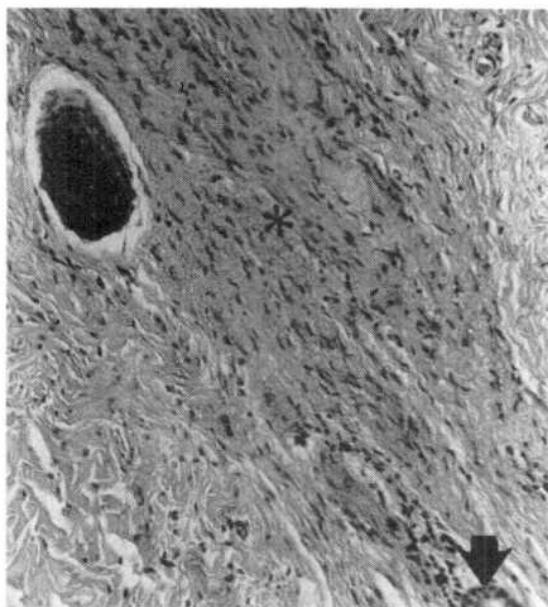


Fig. 5 Nylon suture in rabbit, six-week specimen. Collagen of the residual scar track appears well organised (asterisk) and a persistent area of epithelial ingrowth (arrow) is noted. (H and E, $\times 32$.)

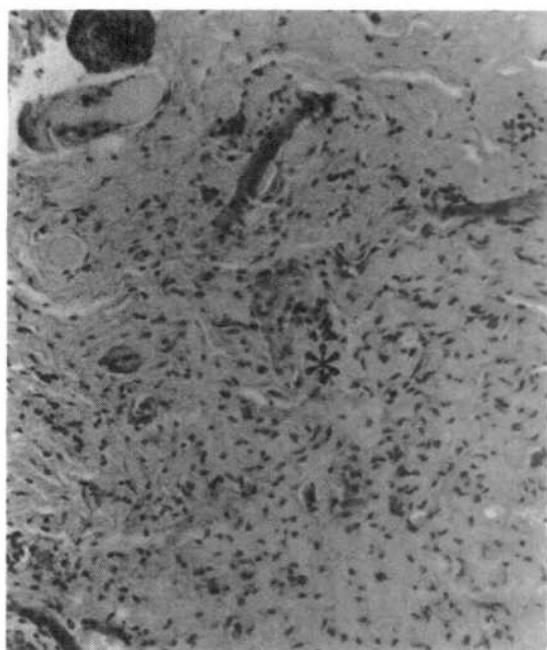


Fig. 6 Chromic gut suture in rabbit for six weeks. Fibroblasts and dense collagen (asterisk) are present within the scar track. (H and E, $\times 32$.)

lower eyelid margin until a more definitive procedure can be performed. After suture removal or dissolution the repair relies on the fibrotic track left behind. In this study both rabbit and human specimens were

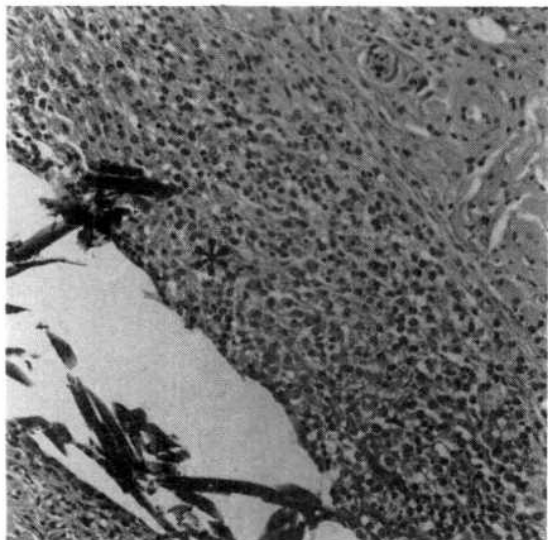


Fig. 7 Silk suture in patient for two weeks. The suture is surrounded by an intense epithelioid cell reaction (asterisk). (H and E, $\times 32$.)



Fig. 8 Nylon suture in patient for two weeks. Collagen formation (asterisk), chronic inflammatory cells (solid arrow), and epithelial ingrowth (hollow arrow) around the suture are seen. (H and E, $\times 32$.)



Fig. 9 Chromic gut suture in human for two weeks. Regular collagen formation by fibroblasts along the suture track is demonstrated (asterisk). Chronic inflammatory cells are evident (arrow). (H and E, $\times 32$.)

examined for scar track formation at varying intervals after suture placement.

Chromic gut, nylon, and silk sutures were studied in rabbit lower eyelids for their ability to create demonstrable fibrous tracks. All three sutures incited inflammatory reactions and fibroblastic activity with collagen formation at two and four weeks. Epithelial ingrowth was noted along the nylon and silk suture tracks as well. At six weeks residual scar tracks were observed for all three sutures.

In the human specimens, silk, nylon and chromic gut all provided an aggressive fibrotic and inflammatory response at two weeks.

In the treatment of involutional entropion an organised thick collagen track is desirable to reinforce the attachments between the inferior tarsus and the

lower eyelid retractors and better to prevent overriding preseptal orbicularis. Clinically, silk rotation sutures are able, at least temporarily, to accomplish this.⁵⁻¹⁰

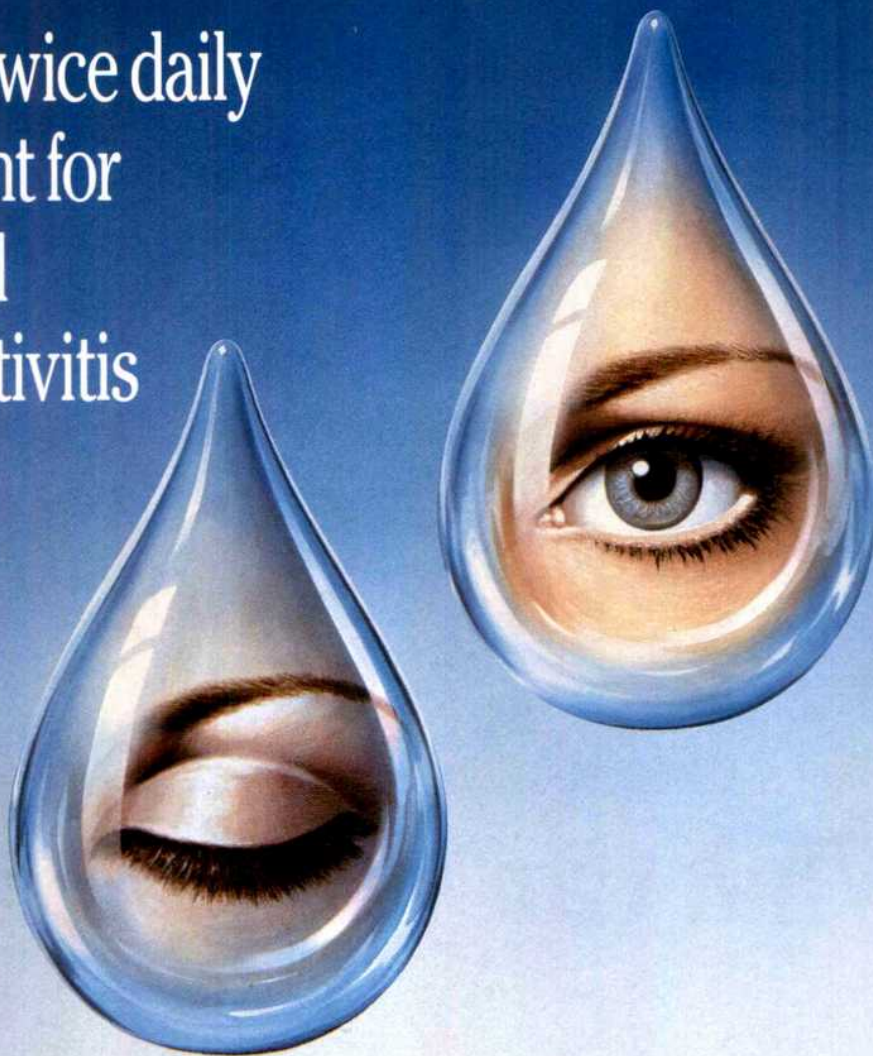
This study shows that nylon, chromic gut, and silk sutures all create histologically similar fibrotic scars along their tracks. The reasons for these fibrotic reactions are not clear. They could be due to an inflammatory response to the suture material itself or to tissue necrosis from suture tension. Whatever the reasons for the scar formation, the tracks should all be sufficient to correct an involutional entropion based on what we already know empirically about silk. Thus hypothetical differences in scar track formation should have a minimal role in the surgeon's choice of suture material. The availability of a doubled armed suture or the need for an absorbable material may in fact be more important considerations in any particular case.

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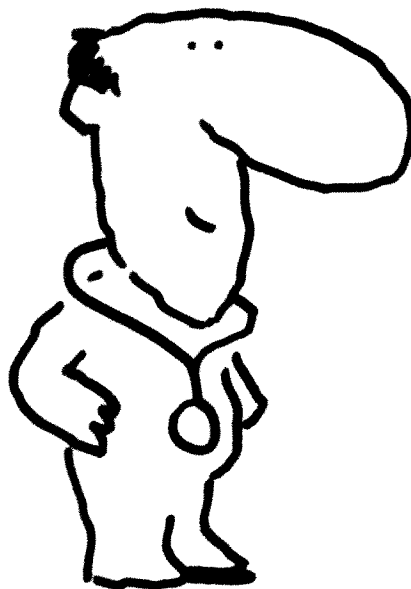
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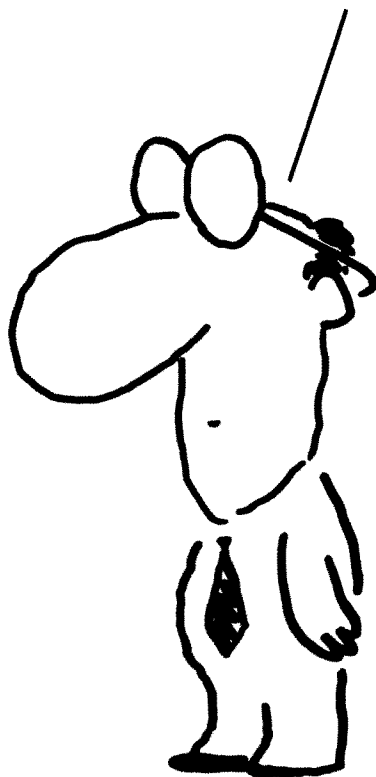
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Passive limitation of adduction after Cüppers's 'Fadenoperation' on medial recti

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SUMMARY In 40 eyes of 20 esotropic subjects in which a 'Fadenoperation' was performed on the medial recti we measured the resistance to ocular rotation in adduction before and after the operation. The difference between the two sets of force measurements demonstrates that the Fadenoperation on medial recti produces a mechanical restriction to adduction which can explain the effect of the surgical procedure on the strabismic deviation.

In 1974 Cüppers described the well known surgical procedure which he named 'Fadenoperation'.¹ The effect of the operation was at first attributed solely to the reduction of the tangential component of the muscle force produced by the posterior fixation.^{1,2} Later it was pointed out³ that several different mechanisms could interact and concur to produce the surgical effect:

- (1) the reduction of the rotational component of the force generated by the muscle;
- (2) the exclusion from activity of a contingent of the muscle fibres;
- (3) a stretching of the muscle owing to the fact that the scleral fixation increases the distance between the origin and the true insertion of the muscle if the true insertion remains in its original position;
- (4) a slack in the muscle fibres posterior to the fixation suture which occurs when the tightening of the suture is made while the muscle is stretched to provide adequate exposure⁴;
- (5) a mechanical restriction to ocular rotation in the field of action of the operated muscle^{5,6} produced by the connective tissue structures, which endeavour to maintain the physiological course of the muscle,⁵ or by a 'reverse leash' mechanism.⁷

All these hypothetical effects were derived from a theoretical analysis of the new mechanical situation

created by the surgical procedure, but so far none of them has been experimentally proved. The present investigation was aimed at ascertaining the existence and the importance of a mechanical restriction to ocular rotation produced by the Fadenoperation.

Materials and methods

In 40 eyes of 20 comitant alternating esotropic patients, in which a Fadenoperation was performed on both medial recti we measured the resistance to passive adduction before and after the operation. The most significant characteristics of the patients are listed in Table 1.

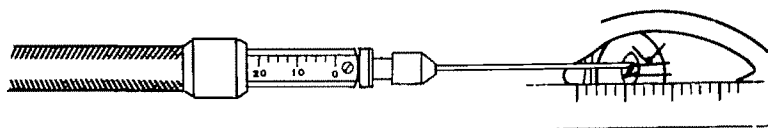
The posterior fixation sutures were placed 14 mm behind the insertion of the medial recti by a technique similar to that originally described by Cüppers.¹ A small recession of the medial recti was

Table 1 Summary of clinical data

Patients: 20 (M:6, F:14)	Eyes: 40
Onset of esotropia (months)	
median: 15	max: 96 min: 0
Age at the operation (years, months)	
median: 3 yr 10 m	max: 11 yr 8 m min: 2 yr 4 m
Maximal ocular deviation at distance (degrees)	
median: 26	max: 38 min: 16
Refraction (spherical equivalent, dioptries)	
median: +3.25	max: +6.25 min: -0.5

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Fig. 1 The experimental set-up.



added in all procedures (3 mm in 16 muscles, 2 mm in 22 muscles, and 1 mm in 2 muscles). Before the operation, in the awake patient, we measured with a ruler the distance between the temporal limbus and the inner canthus when the eye was fixating in a straight ahead position, which we estimated to be a good approximation of the primary position.⁵

In stage 3, plane 2, of halothane general anaesthesia, which was induced without succinylcholine,⁸ we repeated the measurement of the same cantholimbus distance by the same method and at the same observation distance in order to control the paralactic error. In this way we could determine the position of the globe relative to the primary position.

A traction suture was passed through the temporal limbus and a knot made not too far away. The loop of this suture was then hooked with the hook attached to a modified Müller ophthalmodynamometer, previously gas sterilised, and a tangential traction was applied in order to produce a nasal rotation of the globe. A ruler held at the globe surface indicated the size of the nasal displacement of the temporal limbus. The grams of force required for each millimeter of temporal limbus displacement, up to 8 mm, was read by an assistant from the dynamometer (Fig. 1).

The globe was then replaced in the original position and a second set of measurements was obtained. The same procedure was carried out after the completion of the operation, but this time force measurements were recorded in primary position and at 2 mm intervals up to 8 mm of limbus displacement in adduction.

The ophthalmodynamometer was accurately calibrated before every surgical session.

Table 2 Passive resistance to adduction (grams) before and after a Fadenoperation on 40 medial recti

Adduction (mm)	Preop. mean (95% conf. limits)	Postop. mean (95% conf. limits)
0 (primary position)	0 (-)	14.87 (13.13-16.92)
2	4.36 (2.86-6.34)	20.22 (18.31-22.43)
4	10.53 (8.94-12.45)	25.90 (23.52-28.67)
6	13.36 (11.50-15.59)	36.80 (30.02-41.19)
8	18.41 (16.77-20.27)	52.15 (44.97-56.48)

To ascertain the effect of several variables on the resistance to passive adduction before and after the Fadenoperation on medial recti we used analysis of covariance for repeated measurements.⁹ This statistical technique combines the features of the analysis of variance and of regression. It was therefore possible jointly to evaluate the relationship between a continuous response variable and a set of independent variables measured on different scales. In our analysis we considered a mixture of continuous variables (age, onset, and duration of strabismus, pre- and postoperative ocular deviation, postoperative adduction); one 'grouping' factor (sex) and two 'within' factors, namely, the 'adduction' factor with five levels (0, 2, 4, 6, 8 mm of passive adduction) and the 'before and after' factor with two levels (before and after the Fadenoperation).

Rather than the original tension measurements the inverse of these values was employed in the analysis in order to render their distribution approximately gaussian. On the assumption that the distribution of the inverse of the tension values was gaussian, approximate 95% confidence limits were calculated both for the single means at each level of passive adduction and for their difference before and after the Fadenoperation. Back transformation of these values provided the estimates of the 95% confidence limits in the original scale.

The eye position at rest was considered free from error. This is why at this point there is no measure-

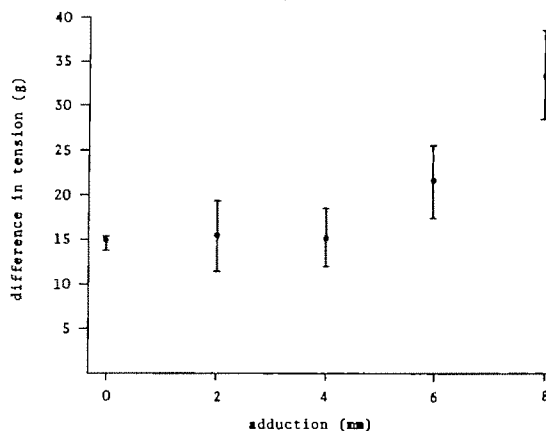


Fig. 2 Estimated differences in tension ($\pm 95\%$ confidence limits) before and after Fadenoperation on 40 medial recti.

ment of variability, and the 95% confidence limits could not be computed.

The P2V Program of the BMDP Statistical Package was used to perform the analysis.

Results

The results of our investigation are presented in Table 2 and Fig. 2. Only the 'within' factors 'adduction' and 'before and after' as well as their interaction proved to be highly significant ($p < 0.0001$). That means that the passive resistance to adduction was influenced by the Fadenoperation on medial recti in a way proportional to the degree of adduction.

The influence of the order independent variables could not be demonstrated at the $p = 0.05$ significance level.

Discussion

The preoperative measurements of passive adduction show a stiffness of about 0.45–0.5 g per degree of adduction. This compares favourably with the values reported in other studies^{8–12} and corroborates the accuracy of our measurement method.

The postoperative measurements show that the Fadenoperation on medial recti produces an augmentation of the passive resistance to adduction which increases with the degree of adduction. The measurements show that in order to keep the eye in the primary position, immediately after the operation, the extraocular muscles should develop a rotational force near to that needed preoperatively to rotate the eye to about 30° of adduction. This could account for the effect of the Fadenoperation in the primary position, which was never completely and satisfactorily explained by other mechanisms. This resistance could also be the cause of the transient divergence which is typically observed at the end of the operation and in the first postoperative days.

The passive resistance to adduction seems to run a decreasing course after the operation, since we usually observed a steady increase of the adduction in the postoperative months (from about 25° immediately after the operation to about 35°–40° after one year). This evolution could be explained by the reduction of the postoperative inflammatory reaction

as well as by a stretching of the connective structures in which the muscle is embedded.

From our study we can conclude that the mechanical restriction to ocular rotation produced by the Fadenoperation has a fundamental role in determining the effect of the operation on the strabismic deviation. In the introduction we mentioned other mechanisms proposed to show how the Fadenoperation could produce a reduction of the rotational force of the muscles. We acknowledge that they can concur to determine the effect of the operation, but we would emphasise that up to now their efficacy has not been experimentally proved.

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Acute acquired comitant esotropia

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SUMMARY Acute acquired comitant esotropia has been used to describe a dramatic onset of a relatively large angle of esotropia with diplopia and minimal refractive error. We describe six children aged 5 to 11 years who developed an acute non-accommodative esotropia with diplopia. Neurological examination, including CT scan, in each of these children gave negative results. We suggest that this is an unusual presentation of esotropia of undetermined aetiology. The diagnosis, clinical characteristics, and management are discussed.

Acute acquired comitant esotropia (AACE) is an unusual presentation of esotropia which occurs in older children and adults. It is characterised by acute onset of esotropia with diplopia. The refractive error is insignificant and neurological examination gives normal results. The purpose of this paper is to discuss the diagnosis and management of this unusual condition in children.

Patients and methods

We reviewed the records of patients aged 3 years or older who presented with the acute onset of diplopia and comitant esotropia from January 1984 to December 1987, at the paediatric ophthalmology services of Wills Eye Hospital, Albany Medical Center, Children's Hospital of New Jersey, and Schneider Children's Hospital. We excluded all patients who had a reduction in their esotropia with hyperopic spectacle correction.

Results

Of the 11 patients aged 3 or older who presented with acute onset of comitant esotropia and diplopia six met the above criteria for inclusion in this study. The patients ranged in age from 5 to 11 years, median 7 years. All complained of diplopia. In three patients the esotropia and diplopia were intermittent initially but became constant within a few weeks. The onset of

esotropia was an average of six months prior to our examination, range one to 10 months. The esodeviation was comitant and ranged from 20 to 55 prism dioptres (Figs. 1,2,3). The near and distance measurements were equal. Visual acuity was 20/20 in all eyes. Ocular rotations, pupils and results of fundus examinations were normal. A cycloplegic retinoscopy under pentolate 1% or 2% was performed on each patient. The full cycloplegic refraction was prescribed for all patients, initially, with no change in the deviation noted (Table 1). None of the patients had a preceding infection or any neurological symptoms. In addition to the ophthalmic examination each child was examined by a paediatric neurologist and underwent CT scanning; all results were within normal limits. Other specific neurological tests in individual cases, as recommended by the paediatric neurologist, were completed. The negative results



Fig. 1 Patient No. 6 in primary gaze.

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Fig. 2 Patient No. 6 in right gaze, illustrating comitance of esotropia.



Fig. 3 Patient No. 6 in the left gaze, illustrating comitance of esotropia.

are listed in Table 1. All six patients underwent a bilateral medial rectus recession appropriate for the amount of esotropia on average eight months after initial presentation, range 3–24 months.

At follow-up ranging from three months to three years the angle has been found to have remained stable at orthophoria, except in one patient who developed a recurrent esotropia of 25 dioptres. This patient was previously described by Goldman and Nelson.¹ The results of sensory tests are listed in Table 2.

Discussion

Previous case reports divide AACE into three types. Burian and Miller² in 1958 reviewed the features of each type of AACE. Type I AACE, first described in 1947 by Swan,³ follows occlusion of one eye or loss of vision in one eye secondary to injury or disease. Von Noorden⁴ postulates that the esotropia is the result of interruption of a previously well functioning fusion mechanism, causing a latent deviation to become manifest. The course of this deviation may be variable, resulting in spontaneous resolution or becoming constant and requiring treatment.

Table 1 Clinical characteristics and neurological testing

Patient	Age	Sex	Refractive error	Neurological testing
1	10	M	Plano Plano	MRI –ve Tensilon –ve CT –ve
2	7	M	OD+1.75 OS+0.75+1.00×180°	MRI –ve CT –ve
3	6	M	OD+1.50 OS+1.50	Spinal tap –ve CT –ve
4	7	F	OD+1.75 OS+1.00	Tensilon –ve CT –ve
5	11	F	OD+1.00 OS+1.00	Tensilon –ve CT –ve
6	10	M	OD–6.75 OS–6.00	CT –ve

Type II AACE, which is also termed the Franceschetti type,^{2,4} is characterised by an acute onset of a relatively large angle of comitant esotropia and diplopia. The refractive error is usually mildly hyperopic but does not influence the angle of deviation. There is no history of infection, and the results of neurological examination are negative. Burian⁵ reported on four patients aged six to 72 years. Their angle of esotropia ranged from 30 to 70 prism dioptres, and treatment with glasses did not improve the angle of esotropia. In one of Burian's patients esotropia began while he was ill with pneumonia.

Type III AACE, reported by Bielschowsky in 1922,⁶ is characterised by the acute onset of esotropia in patients with uncorrected myopia of –5.00 dioptres or more, presumably following physical or mental stress. These patients were esotropic at distance but orthophoric at near vision. The mechanism was thought to be uncorrected myopia with excessive close work, leading to strengthening of the medial recti and weakening of the lateral recti. These patients have subsequently been excluded⁴ from the classification of AACE because the esotropia is present only at distance fixation. These patients are more appropriately classified as having divergence insufficiency.

Our patients had type II AACE with an acute onset of moderate to large angle comitant esotropia

Table 2 Deviation and stereoacuity results

Patient	Surgery after onset (months)	Angle (pre-op.)	Angle (post-op.)	Stereo (post-op.)
1	3	30 ET	Ortho	80 arc s
2	9	25 ET	Ortho	40 arc s
3	12	45 ET	25 ET	Unknown
4	12	45 ET	Ortho	40 arc s
5	6	55 ET	Ortho	40 arc s
6	9	35 ET	Ortho	40 arc s

ET=esotropia.

with diplopia. The refractive correction did not influence the angle of deviation. Unlike Burian's series,³ our patients did not have either preceding or coincidental illness. In all of them the results of neurological examination were normal.

Because of the concern about the possible development of suppression, these patients can be treated with base-out prisms to maintain binocular function until the angle of deviation stabilises. However, four of our six patients had 40 arc seconds of stereoacuity, which would eliminate the possibility of a previous monofixation syndrome that decompensated. The excellent stereopsis also showed that these patients did not develop suppression.

Type II AACE may be a dramatic and alarming condition. We recommend that patients who present with acute onset of diplopia and comitant esotropia receive a complete ophthalmologic and neurological examination and a careful history taken to rule out cyclic esotropia, divergence insufficiency, parietic strabismus, and myasthenia gravis, any of which may also present acutely.¹ Whether further examination including CT scanning, should be performed is still not clear. In our series the results of all neurological tests were negative, but we believe that, owing to the relatively small size of our series, a larger number of patients must be studied before a recommendation to eliminate neurological testing is made. Since invasive

studies (such as Tensilon testing and neuroradiological testing) in children carry some risk, this is an important question to answer. We also suggest that the term AACE type II be reserved for patients with acute onset of diplopia and comitant esotropia unrelated to refractive error and of unknown aetiology.

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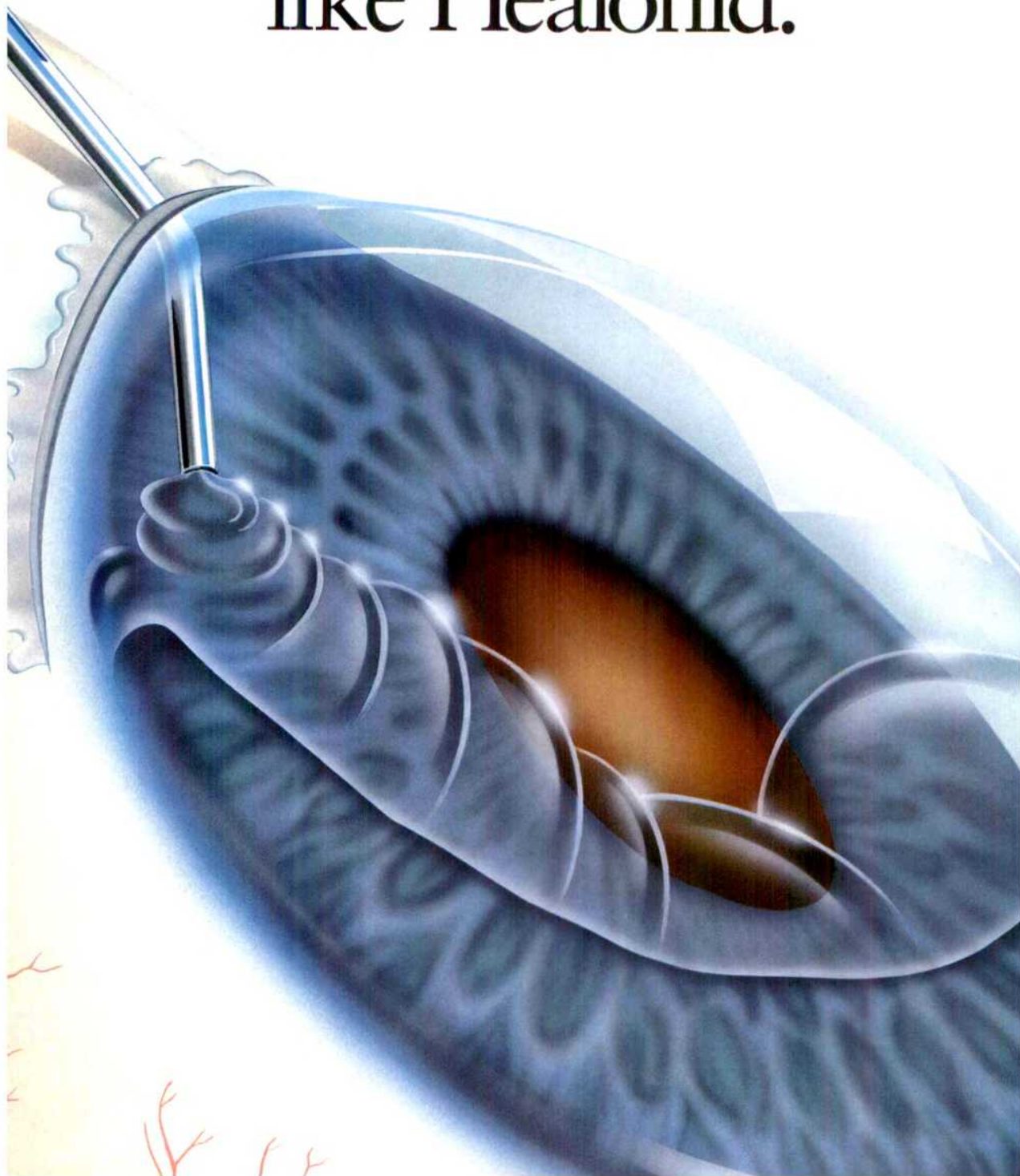
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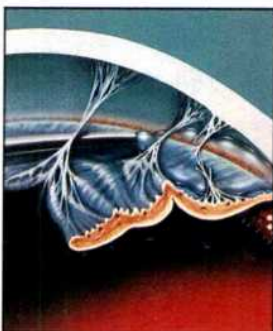
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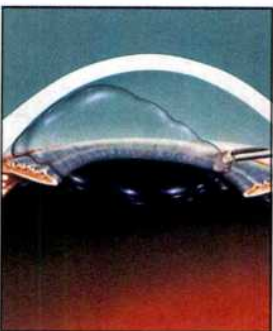
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Clinical criteria for the assessment of disease activity in Graves' ophthalmopathy: a novel approach

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SUMMARY Patients with serious inflammatory Graves' ophthalmopathy should be treated with anti-inflammatory drugs or radiotherapy to prevent complications like fibrosis, while those with non-inflammatory ophthalmopathy may be treated by surgery immediately. It is often difficult, however, to distinguish inflammatory from non-inflammatory Graves' disease. We therefore present a simple *clinical* classification here to differentiate between these two conditions. This classification is based on the classical signs of inflammation—pain, redness, swelling, and impaired function. After two consecutive clinical examinations an 'activity score' can be determined, ranging from 0 to 10 points. In a retrospective study testing the efficacy of this classification we found that patients with an activity score of 3 or more at the beginning of therapy responded well to anti-inflammatory drugs, while those with a lower activity score mostly did not. Comparing the pretreatment activity score with the degree of enlargement of the extraocular muscles on the CT scan, we found a significant correlation between these two parameters: the higher the activity score, the more the enlargement of the muscles. We conclude that this classification facilitates the proper selection of patients for treatment.

Graves' ophthalmopathy appears to be an organ-specific autoimmune disorder.¹ A still unidentified pathogenic process induces swelling, lymphocytic infiltration, and later fibrosis and contractures that restrict the normal function of the extraocular muscles.² Two stages in the development of the disease are generally distinguished: the stage of active inflammation in which the eyes are red and painful, and the quiescent stage in which the eyes are white and unchanging with a painless motility deficit.³

Treatment of serious Graves' ophthalmopathy may be either non-surgical or surgical. Of the non-surgical treatments orally administered steroids or radiotherapy or a combination of both are usually favoured. No agreement on the results of these treatments can be found. Brain⁴ reported immediate beneficial effects on the inflammatory components of the ophthalmopathy after short high doses of corticosteroids. Day and Caroll⁵ noted dramatic improvement of optic neuropathy by this therapy.

McCohaney⁶ stated that extraocular muscle dysfunction at the stage of fibrosis and proptosis does not generally respond well to corticosteroids. However, Wiersinga *et al.*⁷ found a positive response in 66% of all patients treated with prednisone alone. Hurbli *et al.*⁸ found better results with radiation therapy in patients having a short history of Graves' ophthalmopathy than in patients with long-term ocular changes. Apart from basic differences in the definitions of successful treatment among authors these unequal success rates can be explained by the heterogeneity of the patients—patients with inflammatory progressive Graves' ophthalmopathy and those with the non-inflammatory stationary stage of the disease.

The indication for treatment has always been the severity of symptoms (according to the NOSPECS classification*) instead of the rate of progression of the disease. During the initial stage immunosuppres-

*An abridged classification of eye changes in Graves' ophthalmopathy^{9,10}: class (0): no physical signs or symptoms; (1) only signs, no symptoms (signs limited to upper lid retraction, stare, and lid lag); (2) soft-tissue involvement (symptoms and signs); (3) proptosis; (4) extraocular muscle movement; (5) corneal involvement; (6) sight loss (optic nerve involvement).

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sive treatment or radiotherapy is logical and inhibits the inflammatory process. Once fibrosis has taken place, this kind of treatment is useless. Surgery can deal with the residual sequelae successfully. It is therefore imperative to know whether a patient has active or quiescent Graves' ophthalmopathy.

To match appropriate therapy to the patients we propose a clinical classification to discriminate easily between the active and quiescent stages of the disease. This system is based on the well known signs of acute inflammation: pain (Latin: dolor), redness (rubor), swelling (tumor), and impaired function (functio laesa), defined by Celsus and Galen centuries ago.

Clinical classification for disease activity

Patients with Graves' ophthalmopathy complain of pain, a burning sensation, excessive lacrimation, photophobia, swelling of the eyelids, proptosis, double vision, and visual impairment. These symptoms and signs are related to the classical signs of inflammation (Table 1).

In Graves' ophthalmopathy several kinds of pain can be distinguished. One kind of pain arises from the stretching of the inflamed muscle(s), especially on attempted upgaze.⁹ Another sort of pain is caused by the rise in intraorbital pressure, when the orbital tissues expand through fluid accumulation and cellular infiltration. This is felt as a painful, oppressive feeling on or behind the globes. When asked, most patients can discriminate well between these two kinds of pain. The 'stretching pain' cannot be provoked by digital pressing on the eyeball, as would be expected if it were a manifestation of the raised intraorbital pressure. Both kinds of pain are the first



Fig. 1 Patient with inflammatory Graves' ophthalmopathy, showing redness of the eyelids and diffuse redness of the conjunctiva. Oedema of the eyelids is also clearly visible.

symptoms to disappear after anti-inflammatory treatment. We therefore consider these kinds of pain to be directly related to the inflammation in the orbit and thus useful in assessing inflammatory activity. They differ from pain caused by corneal defects, pain due to a spasm of the orbicularis muscle secondary to photophobia, or pain in the context of asthenopia because of a changed refraction. We consider these last symptoms to be epiphenomena and therefore not useful in assessing the disease activity.

Redness as an expression of inflammation is caused by vasodilatation. In Graves' ophthalmopathy this is seen as redness of the eyelids and over the conjunctiva (Fig. 1). These signs must be differentiated from the redness accompanying exposure keratitis and the grossly dilated vessels over the insertions of the extraocular muscles. The latter condition is seen both in active and in quiescent Graves' ophthalmopathy.

Swelling in Graves' ophthalmopathy is seen as chemosis (oedema of the conjunctiva) and a swollen caruncle (Fig. 2). Both are signs of activity. Swollen

Table 1 Proposed classification system to assess disease activity in Graves' ophthalmopathy

Pain	
	painful, oppressive feeling on or behind the globe, pain on attempted up, side, or down gaze
Redness	
	redness of the eyelid(s), diffuse redness of the conjunctiva
Swelling	
	Chemosis, swollen caruncle oedema of the eyelid(s) increase of proptosis of 2 mm or more during a period between 1 and 3 months
Impaired function	
	decrease in visual acuity of 1 or more lines on the Snellen chart (using a pinhole) during a period between 1 and 3 months decrease of eye movements in any direction equal to or more than 5 degrees during a period of time between 1 and 3 months

For each of the signs present one point is given. The sum of these points defines the activity score.



Fig. 2 Patient with inflammatory Graves' ophthalmopathy, showing grossly enlarged caruncles and oedema of the eyelids.



Fig. 3 Patient with 'burnt out' Graves' ophthalmopathy. The swelling of the eyelids is not caused by oedema.

eyelids can be caused by oedema, fat prolapse through the orbital septum, or fibrotic degeneration (Fig. 3). Here only eyelid oedema should be considered a sign of inflammation. To differentiate oedema from other causes of eyelid swelling palpation and illumination of the eyelids with a torch are mandatory.

In Graves' ophthalmopathy inflammation causes fluid accumulation and cellular infiltration in the orbit, later to be followed by fibrotic tissue. Proptosis and swelling of the eyelids are the result of the entire process. Therefore proptosis and eyelid swelling are not in themselves signs of acute inflammation. However, increasing proptosis in this context is a proof of it. A test-retest error of 2 mm is usually cited as the limit of exophthalmometer accuracy.^{10,11} We therefore consider an increase in proptosis of 2 or more millimetres to be a positive sign of disease activity.

Visual impairment in Graves' ophthalmopathy, resulting from dysfunction of the optic nerve, is caused by raised intraorbital pressure due to the inflammatory process.¹² Therefore a decrease of visual acuity as a result of optic compression is a sign of disease activity. However, a decrease of visual acuity due to corneal defects cannot be considered an early sign of active Graves' disease. Corneal defects are most probably caused by increased width of the palpebral fissure, which accelerates tear film evaporation, thus increasing tear film osmolarity, with resulting ocular damage.¹³ That is why we consider corneal involvement to be an epiphenomenon. A decrease in eye movements implies that the extraocular muscle function is progressively impaired. It can therefore be regarded as a sign of disease activity.

To detect an increase in proptosis or a decrease in eye movements or visual acuity over a span of time at least two different consecutive examinations are

necessary. In view of the natural history of Graves' ophthalmopathy we consider that the interval between these examinations should be at least one and not more than three months.

Pilot study to test efficacy of classification

The patients' records from an ongoing prospective, randomised, clinical trial to compare the efficacy, safety, and tolerability of cyclosporin and oral prednisone in severe Graves' ophthalmopathy¹⁴ were used for this purpose. In this study 26 consecutive patients with serious Graves' ophthalmopathy, defined as falling into NOSPECS categories 2c, 3b, 3c, 4b, 4c, 5a, 5b, 5c, or 6a, were treated with oral prednisone or cyclosporin for a period of 12 weeks. These patients were euthyroid for more than two months when they started the trial. They had had no previous eye treatment other than local measures. Eighteen were female and eight male. Their ages ranged from 23 to 70 years.

The treatment consisted of 60 mg prednisone/day during the first two weeks, 40 mg during the next two weeks, 30 mg during the next four weeks, and 20 mg during the last four weeks, then tapering off, or cyclosporin 7.5 mg/kg bodyweight/day for 12 weeks. When the therapeutic outcome after 12 weeks was considered unsuccessful, the patients were treated for another 12 weeks with a combination of both oral prednisone (20 mg/day) and cyclosporin (in the same dosage as mentioned above). After 24 weeks the final outcome was evaluated. The success or failure of treatment was defined as shown in Table 2. Patients were examined before and at the beginning of therapy and after 1, 3, 4, and 6 months. Apart from classifying each patient in the NOSPECS system in each category, the visual acuity, proptosis, and eye movements were measured and eyelid oedema and chemosis recorded. At each visit photographs of the face were taken and the patients were asked about their complaints. Coronal CT scans of the orbits were carried out at the beginning of treatment.

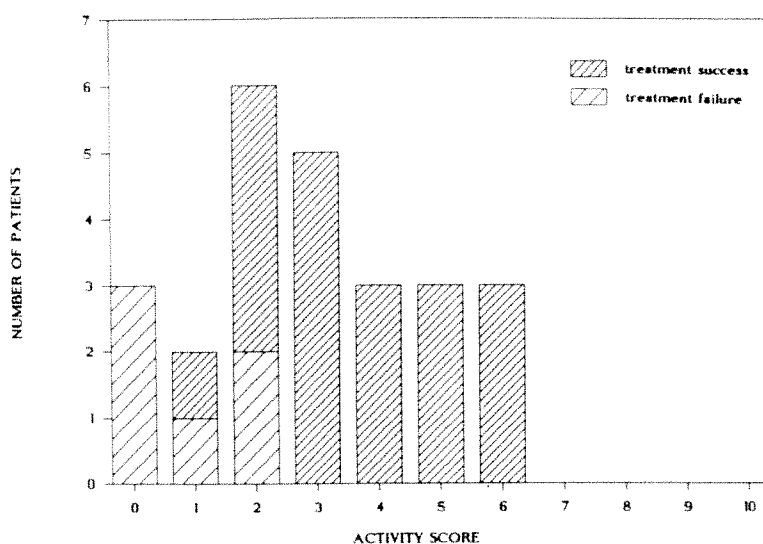
The definitions of pain, as given in our scoring classification, could not be applied, as we were using

Table 2 Definitions of success and failure of treatment in Graves' ophthalmopathy

Success	A decrease (compared to baseline) in NOSPECS class or, if this did not occur, a decrease in grade within a class
Failure	An increase (compared to baseline) in NOSPECS class or, if this did not occur in grade within a class, or no change in NOSPECS class or grade

If both decreases and increases occurred in different classes, the change in the highest class was evaluated for therapeutic outcome.

Fig. 4 Relationship between activity score and number of patients treated for serious Graves' ophthalmopathy.



retrospective data, in which this item had not been planned for. However, all other signs of clinical activity could be assessed from the data.

The results of this study are shown in Fig. 4 and Table 3. After 24 weeks of therapy 19 out of 26 patients with serious Graves' ophthalmopathy had improved according to our predefined parameters and described standards. One patient (No. 24) underwent orbital decompression before the final evaluation of medical treatment was done, because of increasing visual impairment due to optic neuropathy (and was therefore not incorporated in Fig. 4). Three patients showed a worsening of their ophthalmopathy during treatment. They had an activity score of 1 or 2 points. The condition of the remaining

three patients, all of them with an activity score of zero, did not change.

The degree of extraocular muscle enlargement on the orbital coronal CT scan was assessed in a rating system of 5 points (0: no enlarged muscles; 5: grossly enlarged muscles) by an ophthalmologist who was not informed about the activity score. By linear correlation and regression analysis a significant correlation was found between the extraocular muscle size and our activity score ($r=0.52$, volume = $1.9+0.31 \times \text{activity score}$, $p=0.007$). The relationships between muscle size and the activity score will be studied in more detail in future prospective studies.

Fig. 4 suggests that the clinical activity score is

Table 3 Sex, age, relative incidence of disease activity signs, activity score, therapy, and results of therapy in 26 patients treated for serious Graves' ophthalmopathy

Patient number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24*	25	26
Sex	F	F	F	M	F	F	F	M	F	F	F	M	F	F	M	F	F	F	M	F	M	M	F	F	F	M
Age	67	55	39	68	57	54	52	70	54	54	44	40	23	52	62	58	46	36	47	37	54	60	44	43	40	64
Pain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Redness of eyelids	+		+	+	+			+	+	+	+		+		+	+	+		+	+	+	+		+		+
Redness of conjunctiva			+	+				+		+					+	+	+		+	+	+	+		+		
Chemosis	+			+											+	+	+			+	+	+	+	+	+	+
Swollen caruncula																+	+			+	+	+	+	+	+	+
Eyelid oedema				+	+	+		+		+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+
Increase proptosis			+																							
Decrease in VA			+	+	+			+	+																	
Decrease in motility																										
Activity score	3	2	6	6	3	1	2	5	1	3	2	0	3	0	4	2	6	0	4	5	4	5	2	8	3	2
Therapy	D	D	C	A	C	A	B	D	D	C	A	D	A	C	D	D	A	D	A	D	A	D	C	C	B	B
Results of therapy	S	S	S	S	S	S	S	S	F	S	S	F	S	F	S	F	S	F	S	S	S	S	F	S	S	S

*Patient No. 24 underwent orbital decompression before the final evaluation of medical treatment was made.

F=female. M=male.

A=prednisone. B=cyclosporin. C=prednisone first, then cyclosporin added. D=cyclosporin first, then prednisone added.

S=treatment success. F=treatment failure.

helpful in predicting the therapeutic outcome of immunosuppressive treatment in Graves' ophthalmopathy. In patients with an activity score of zero no change of the ocular condition could be demonstrated. Patients with a pretreatment activity score of less than 2 points showed no improvement, whereas patients with 3 or more points did improve on immunosuppressive treatment. In patients with an activity score of 2 points the result of this treatment could not be predicted.

Discussion

We propose a classification system for disease activity of Graves' ophthalmopathy which is easily manageable and entirely *clinical*, making it applicable without the use of special instruments. For this reason, the item 'heat' (Latin: calor), also one of the classical signs of acute inflammation, has been omitted, as the examiner would have difficulty diagnosing it without sophisticated instruments.

In the past patients have been treated with steroids and radiotherapy because of serious but not necessarily active Graves' ophthalmopathy. Our study suggests a positive correlation between our clinical activity score and a final favourable therapeutic outcome. This implies that patients with an activity score of 3 or more can expect beneficial effects from medical treatment. Those with a zero activity score should be spared from radiotherapy or steroids, of which the substantial side effects must not be forgotten.¹⁴ They should be treated surgically. It is generally accepted that a period of at least six months has to elapse before surgical procedures can be applied, provided that no change in the NOSPECS classification has been observed. With our classification system this period may be considerably reduced. After two clinical examinations a few months apart disease activity can be assessed.

Support for the need of the above mentioned classification system can be derived from the literature. In 1969 Werner,¹⁵ as chairman of the American Thyroid Association ad hoc committee on eye disease, introduced the NOSPECS classification system for Graves' ophthalmopathy to summarise the most important symptoms once the diagnosis had been made. This system was modified in 1977.¹⁶ Although Werner's classification has been demonstrated to be of value for studying series of patients with comparable Graves' ophthalmopathy and for defining 'success and failure' in the treatment of the disease, it does not provide a means of distinguishing inflammatory progressive from non-inflammatory stationary Graves' ophthalmopathy. It is therefore of no help in deciding how and when to treat a patient. This is substantially illustrated by Figs. 1 and 3. Both

patients had the same NOSPECS classification (namely, 2/2, 3/1, 4/2, 5/0, 6/0). The first patient (Fig. 1) clearly had active Graves' disease, the second had not.

Van Dijk,³ questioning the fact that the modified NOSPECS classification system no longer allowed disease activity to be specified, has proposed a second modification of the original classification, including a restoration of the listing of soft tissue signs. For class 2 he introduced the mnemonic RELIEF, trying to include designators of activity of the orbital process in the NOSPECS classification system. Although we agree that some of his designators clearly describe activity (for example, oedema of the caruncle, conjunctiva, and eyelid, and redness of the conjunctiva), other important symptoms and signs are omitted (for example, pain, redness of the eyelid, increase in proptosis, and impaired function), while finally two signs of questionable usefulness are mentioned (namely, resistance to retrodisplacement of the eye and lacrimal gland enlargement). We do not contest that these signs actually may occur in Graves' ophthalmopathy, but why should they indicate disease activity? Besides, according to Frueh *et al.*¹⁷ digital estimation of the resistance to retropulsion does not reliably suggest the measured forces. We believe that only eyelid swelling caused by oedema can be considered as a sign of activity, while fullness caused by a fat prolapse or infiltration cannot.

Kahaly *et al.*¹⁸ determined an activity score from the patient's history, clinical findings, and results of laboratory and imaging techniques. In this system signs and epiphenomena, such as eyelid closure and photosensitivity, are confused, while unchanging double vision and proptosis are included as signs of activity.

Sergott *et al.*,⁹ attempting to devise a disease activity index for Graves' ophthalmopathy to correlate with immunological parameters, found five clinical signs the best indicators of active, progressive ophthalmopathy. We have objections against two of these indicators. The sign of resistance to retrodisplacement has been discussed above. From our clinical experience we conclude that dilated blood vessels over the insertions of the horizontal extraocular muscles are a sign of both progressive and quiescent Graves' ophthalmopathy.

In our classification of disease activity we did not mention loss of colour vision because we consider that testing patients with Ishihara pseudoisochromatic colour plates gives less reproducible results and does not provide more information than already gathered by testing the visual acuity.

Although we are aware of the limitations of our pilot study, the results encouraged us to start a

prospective study to show that our classification system is easily managed and increases the success rate of anti-inflammatory treatment in active Graves' ophthalmopathy.

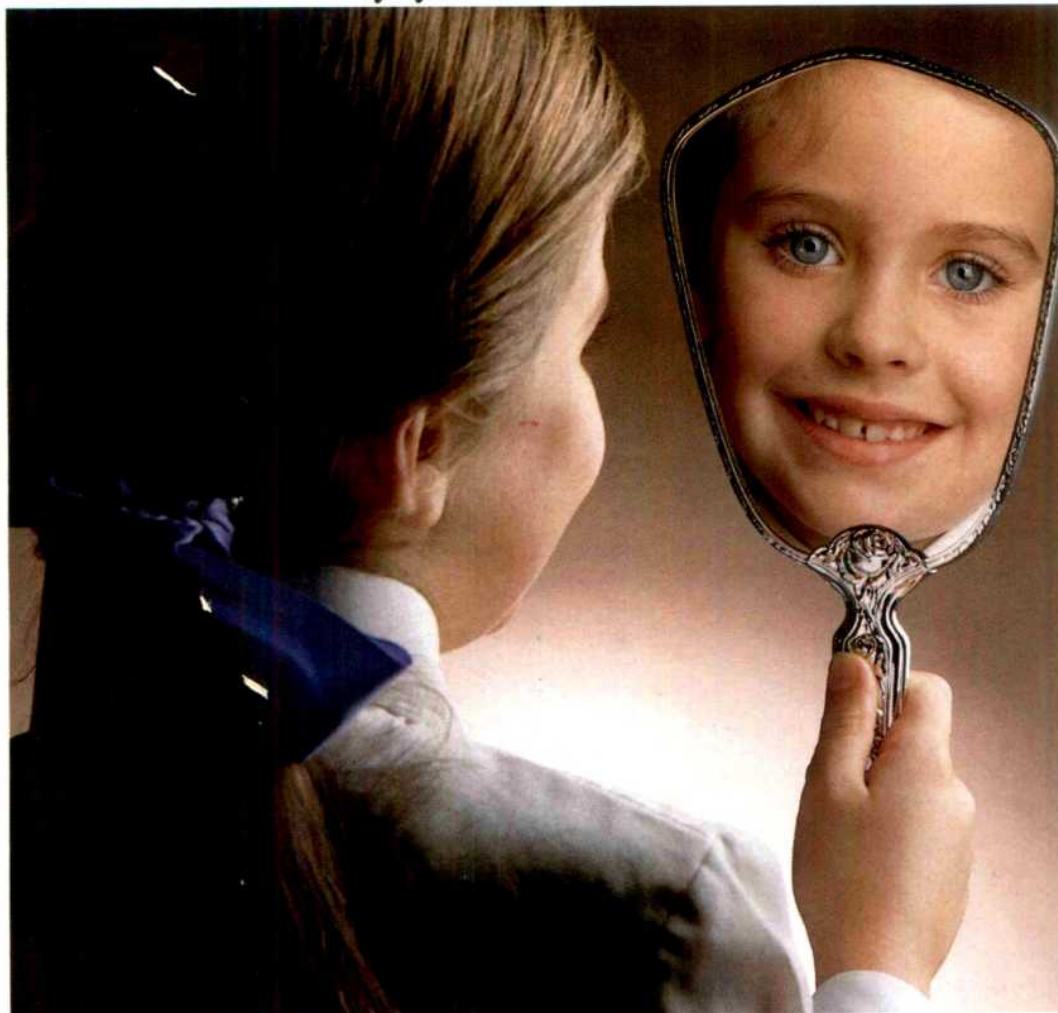
We thank Mr P Y Moriarty, ophthalmic surgeon, for carefully reading and commenting on the manuscript.

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Technical Data Sheet

COATED VICRYL* (POLYGLACTIN 910) Sterilised Braided Synthetic Absorbable Suture

Presentation

The basic VICRYL (Polyglactin 910) Suture is prepared from a copolymer of glycolide and lactide. The substances are derived respectively from glycolic and lactic acids. The empirical formula of the copolymer is $(C_2H_2O_2)_m(C_3H_4O_2)_n$.

Coated VICRYL (Polyglactin 910) Sutures are obtained by coating the braided suture material with a mixture composed of a copolymer of glycolide and lactide and an equal amount of calcium stearate. This coating does not affect the biological properties of the suture.

Coated VICRYL (Polyglactin 910) Sutures are coloured by adding D & C Violet No. 2 during polymerisation of the lactide and glycolide. Sutures may also be manufactured in the undyed form.

These sutures are relatively inert, nonantigenic, nonpyrogenic and elicit only a mild tissue reaction during absorption.

Action: Two important characteristics describe the in vivo behaviour of absorbable sutures. The first of these is tensile strength retention and the second, absorption rate or loss of mass.

Subcutaneous tissue implantation studies of Coated VICRYL Suture in rats show at two weeks post-implantation approximately 55% of its original tensile strength remains, while at three weeks approximately 20% of its original strength is retained.

Intramuscular implantation studies in rats show that the absorption of these sutures is minimal until about the 40th post-implantation day. Absorption is essentially complete between the 60th and 90th days.

Uses

Coated VICRYL synthetic absorbable sutures are intended for use where an absorbable suture or ligature is indicated.

Dosage and Administration

By implantation.

Contra-Indications, Warnings, etc.

These sutures, being absorbable, should not be used where extended approximation of tissues under stress is required.

Sutures placed in skin and conjunctiva may cause localised irritation if left in place for longer than 7 days and should be removed as indicated.

At the discretion of the surgeon, appropriate non-absorbable sutures may be used to provide additional wound support when Coated VICRYL sutures are used in ophthalmic procedures.

The safety and effectiveness of Coated VICRYL (Polyglactin 910) Sutures in neural tissue and in cardiovascular tissue have not been established.

Pharmaceutical Precautions

Do not re-sterilise.

Legal Category

Not applicable

Package Quantities

Various lengths of material packaged in sealed aluminium foil sachets. This primary pack is contained in a peel-apart secondary pack. The unit of sale is 10 or 12 packs contained in a film wrapped drawer style carton.

Further Information

No suture related adverse reactions were reported during clinical trials, although a number of minor reactions were classified as being of unknown cause.

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Use of limbal ring-rod for radiological localisation of ocular foreign body

POON KWONG-YAM

From Hong Kong Government Ophthalmic Service

SUMMARY The limbal ring-rod and the proportional geometric drawing method provide a simple, inexpensive, and fairly accurate measure for the radiological localisation of ocular foreign bodies, and the results simulate those of orbital tomography.

X-raying the orbit, giving frontal and lateral views with the limbal ring,¹⁻⁶ is a simple procedure for the diagnosis and localisation of ocular foreign bodies. However, misinterpretation is not uncommon because of the x-ray magnification, the measuring method, and the direction of gaze^{1,2,7} of the examined eye. To obtain a more accurate localisation a limbal ring-rod and a measuring method comprising proportional geometric drawing have been used in the Government Ophthalmic Service since June 1987.

Material and methods

The limbal ring-rod consists of a limbal ring with a perpendicular rod whose length equals the diameter of the ring. The diameter of the ring is half the diameter of the schematic eye^{1,2,4,8} and is 12 mm in length (Fig. 1).

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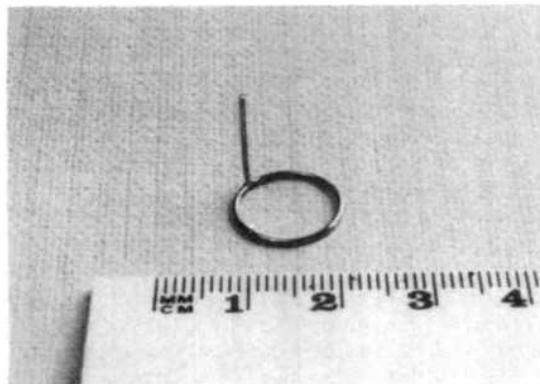


Fig. 1 Limbal ring-rod.

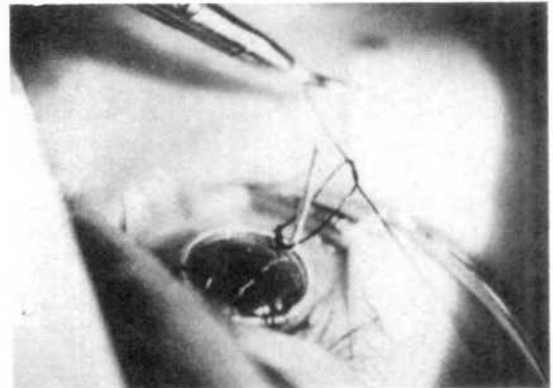


Fig. 2 The rod is stitched at the 6 o'clock position.

INSERTION OF LIMBAL RING-ROD

The limbal ring-rod is sutured onto the limbus with the rod fixed at the 6 o'clock position (Fig. 2). The eye can close and move freely while an x-ray is being taken (Fig. 3).

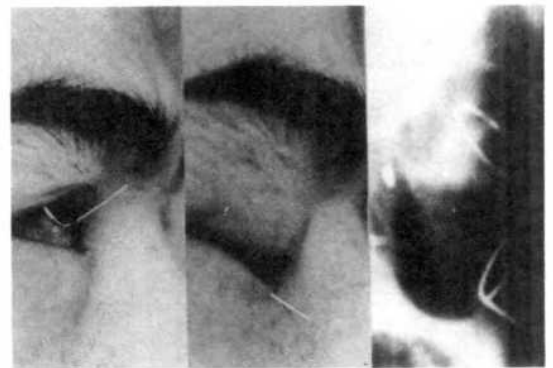


Fig. 3 The eye can move freely.

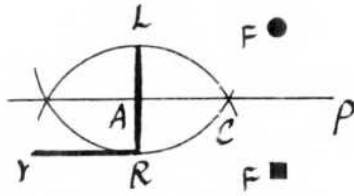


Fig. 4 Geometric construction on lateral view. AP is a bisector of the image of the limbal ring LR. C is the centre of the schematic eye in proportion.

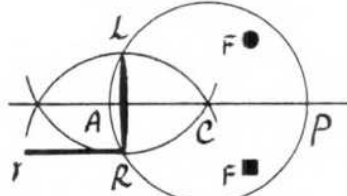


Fig. 5 The greatest circumference of the schematic eye in lateral view is produced with centre at C and radius CL ($CL=CR=LR$).

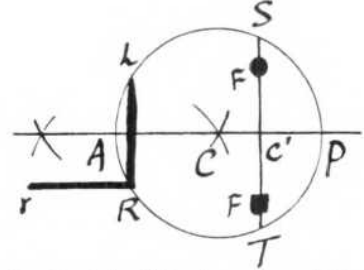


Fig. 6 A line ST is drawn through the image of the foreign body F(s) perpendicular to AP. ST is a tomographic plane in lateral view. C' is the centre of this tomographic plane.

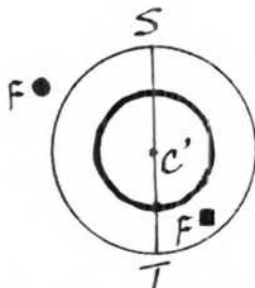


Fig. 7 Frontal view. The eye is looking straight ahead. In practice films of this sort are rarely seen.

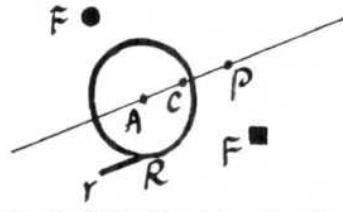


Fig. 8 Geometric construction of frontal view with the eye is not looking straight ahead. AP is parallel to the rod rR through the centre of the ring. $AP=2rR$.

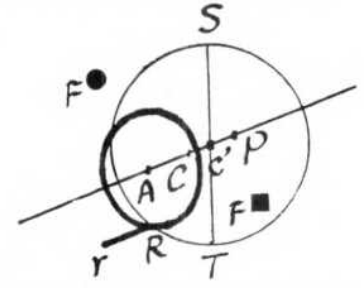


Fig. 9 $AC':AP$ is identical to that in the lateral view as in Fig. 5. ST is a coronal tomographic plane with C' as centre and radius SC' measured from the lateral view as in Fig. 6.

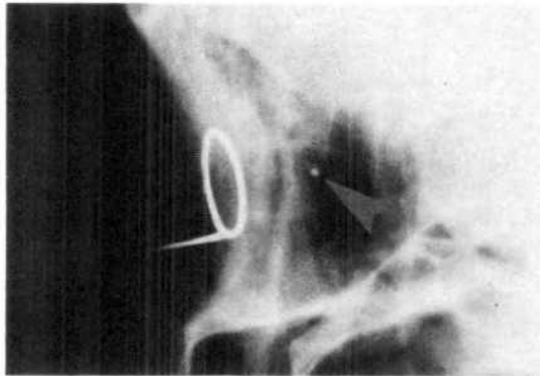


Fig. 10 In Fig. 9, if the limbal ring was used without the rod, the intraocular foreign body would be misinterpreted as an extraocular foreign body, and vice versa.

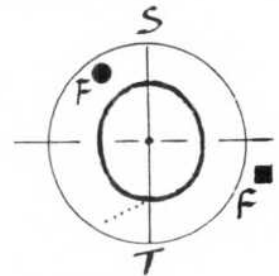


Fig. 11 The foreign body F is situated near the equator.

PROPORTIONAL GEOMETRIC DRAWING

A geometric drawing is made on the films directly or on paper copies of the films.

On the lateral view film the perpendicular bisector of the ring LR gives the corneal axis AP (Fig. 4). The greatest circumference of the schematic eye in lateral view is produced with centre at C and radius CL ($CL=CR=LR$) (Fig. 5).

A line is drawn through the image of the foreign body (or bodies) F(s) perpendicular to AP, intersecting at C' and meeting the circle at S and T. ST is a coronal tomographic plane with C' as centre in the lateral view of the schematic eye (Fig. 6).

On the frontal view film, if the eye was looking straight ahead while an x-ray was taken, the image of

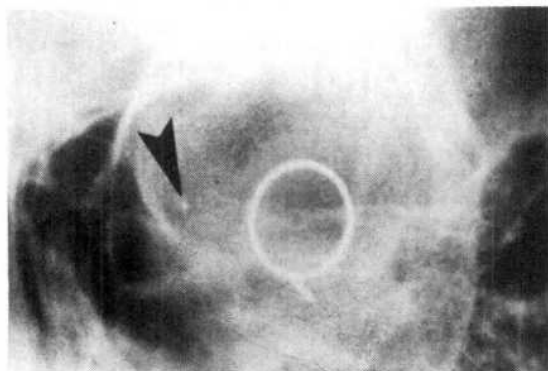


Fig. 12 The foreign body F is situated at the 9 o'clock position.

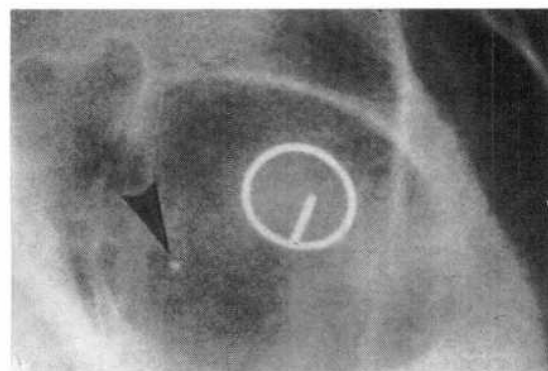


Fig. 13 The foreign body F is situated at the 9 o'clock position.

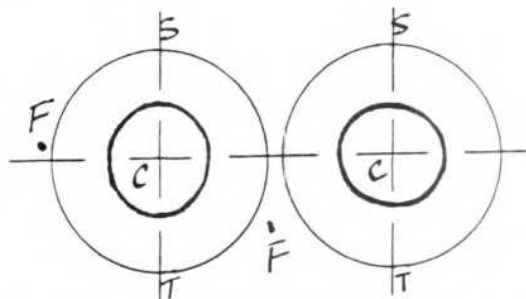


Fig. 14 If a limbal ring is used without a rod, the foreign body F cannot be located.

the rod would appear as a dot, and the corneal axis is also a dot. Hence all coronal tomographic planes (different diameter ST) appear as circles concentric with the ring. In practice, however, these films are rarely seen (Fig. 7).

The images of the rod usually appear with different directions and length, indicating that the eye was not looking straight ahead while the x-ray was being taken. A line is drawn parallel to the rod rR through A, the centre of the ring, and the length AP is made equal to twice the length of the rod rR ($AP=2rR$). The mid point C of AP is the centre of the schematic eye (Fig. 8).

Next, the point C' on AP is marked so that the ratio of the lengths $AC':AP$ is identical to that in the lateral view shown in Fig. 6. With C' as the centre a circle is drawn with radius SC' measured from the lateral view as in Fig. 6. The coronal tomographic plane where the foreign body (or bodies) F(s) lies is produced (Fig. 9).

Results

If the foreign body F is situated inside the coronal tomographic plane of the schematic eye, it is intraocular foreign body; if outside the schematic eye, it is an extraocular foreign body. The foreign body can be located by the geometric drawings.

Discussion

As regards the image of the rod, we have information about the direction and the corresponding length of the anteroposterior axis of the schematic eye. Hence the coronal tomographic plane where the foreign body is situated can be constructed by the proportional geometric drawing method. Whatever the direction of the rod, the position of the foreign body in the coronal tomographic plane remains unchanged. If the limbal ring was used without the rod, only the centre of the ring could be used to construct the coronal planes; an intraocular foreign

body would be misinterpreted as an extraocular foreign body, and vice versa (Fig. 10).

It should be noted that the size of the schematic eye is related to the size of image of the ring. Thus the influence of radiological magnification^{1,2,4,7} on the localisation of an ocular foreign body can be eliminated (usually the magnification is 15–30%).

Case reports

Two cases are reported to illustrate the localisation method.

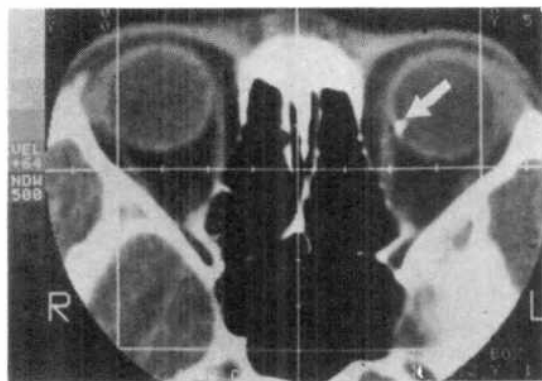


Fig. 15 CT scan.

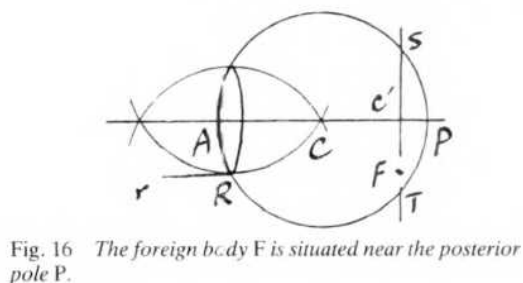
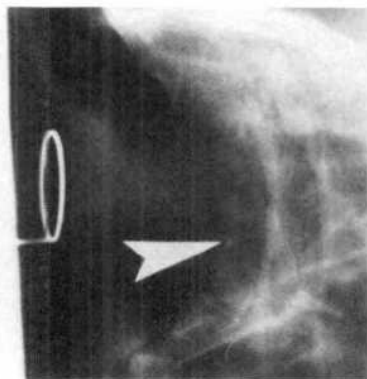


Fig. 16 The foreign body F is situated near the posterior pole P.

CASE A

A lateral view (Fig. 11) showed the left eye with a foreign body image near the equator. Two anteroposterior views (Figs. 12, 13) confirmed that the eye was not looking straight ahead. The foreign body was inside the coronal tomographic plane of the eye at the 9 o'clock position, near the wall. It is clear that, whatever the direction of the rod, the position of the foreign body in the coronal plane remains unchanged. If a limbal ring was used without a rod, Figs. 12 and 13 would appear as in Fig. 14. The foreign body F could not be localised because the anteroposterior axis AP could not be found.

A radiological report can be made: Intraocular foreign body in left eye near the equator at the 9 o'clock position near the wall. A CT scan,^{3,7} horizontal section (Fig. 15) confirmed the presence of the foreign body. A blood clot in the vitreous at the 9 o'clock equator was also evident.

Surgical removal of the foreign body was carried out with a magnet through a sclerotomy at the equator at the 9 o'clock position.

CASE B

A lateral view (Fig. 16) showed the image of a foreign body in the left eye near the posterior pole. Two anteroposterior views (Figs. 17, 18) showed that the foreign body was inside the coronal plane of the schematic eye at the 6 o'clock position near the wall. If the limbal ring was used without a rod, Figs. 17 and 18 would appear as in Fig. 19. The foreign body F could not be localised.

A radiological report can be made: Intraocular foreign body in the left eye near the posterior pole at the 6 o'clock position near the wall. A CT scan, horizontal and coronal sections (Fig. 20), incorrectly showed that the foreign body was near the anterior pole. The error was due to the fact that the patient was looking upwards when the scan was taken, with the result that the lens shadow was in the same plane as the foreign body image in coronal section. The left fundus showed a blood clot in the vitreous.

Surgical removal of the foreign body was carried out by means of a posterior vitrectomy.

Conclusion

The advantages of the limbal ring-rod and the proportional geometric drawing method for localising ocular foreign bodies are, firstly, accuracy. This method allows the coronal plane to be obtained from a schematic eye, thus providing the information obtained from orbital tomography. From the image of the rod the direction and apparent length of the anteroposterior axis of the eyeball can be constructed in a way that is not affected either by movement of the eyeball or by x-ray magnification.

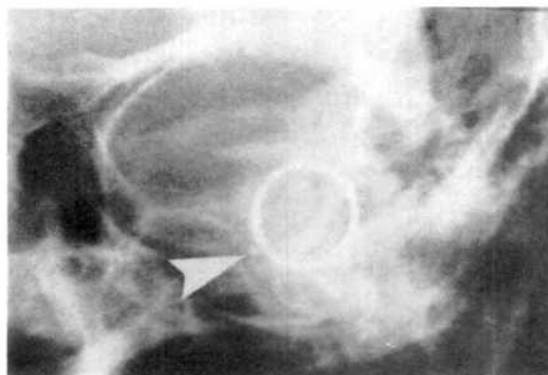


Fig. 17 The foreign body F is situated at the 6 o'clock position.

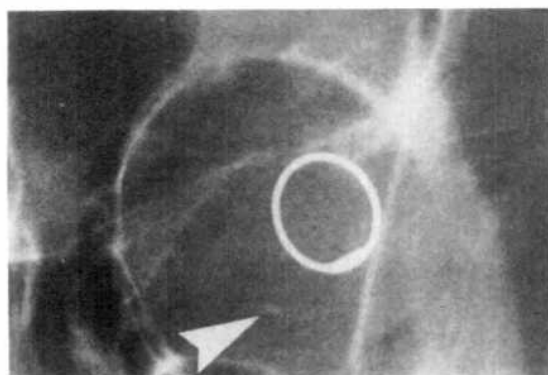


Fig. 18 The foreign body F is situated at the 6 o'clock position.

However, the accuracy could be reduced as follows: (1) Inaccurate transfer of images from the x-ray film on to paper. (2) Loosening of the stitches holding the limbal ring-rod on to the limbus. If the stitches become loose, the rod will move away from

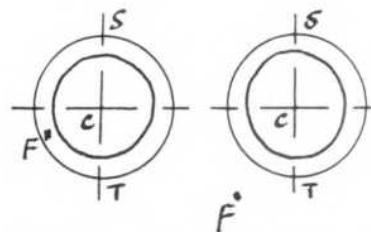


Fig. 19 If a limited ring is used without a rod, the foreign body F cannot be located.

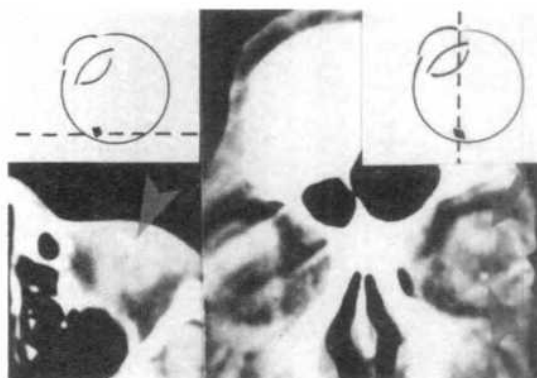


Fig. 20 CT scan. The patient was looking upwards when the scan was taken, with the result that the lens shadow is in the same plane as the foreign body image in coronal section. An intraocular foreign body in the posterior vitreous of left eye would be misinterpreted as in anterior vitreous.

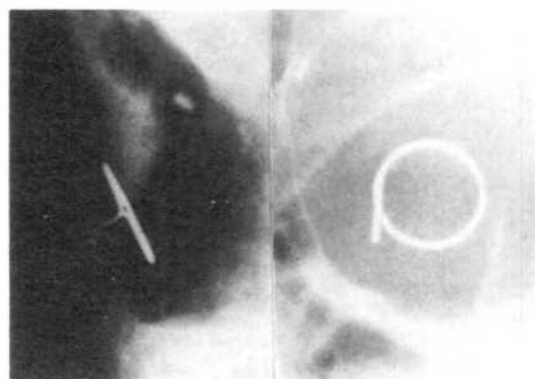


Fig. 21 Loosening of the stitches holding the limbal ring-rod on to the limbus.

the 6 o'clock position; this will be shown on the x-ray films (Fig. 21). (3) The diameter of the patient's eye may be different from that of the schematic eye.

Secondly, the method is simple and inexpensive. This method allows foreign bodies to be localised and hence removed in poorly equipped hospitals.

I thank the Hong Kong Government Ophthalmic Service for providing facilities for the development of this method, and I also thank Dr T K C Liu, consultant ophthalmologist, for his support of this work.

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Assessment of visual function in suspected ocular malingering

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SUMMARY Three new techniques are presented for assessing visual acuity in the presence of suspected malingering. The first technique is based on the preferential looking method commonly used to test acuity in infants. The second uses polarising filters to present stimuli briefly to both eyes or to each eye alone, without the patient's being aware of which eye is tested. The third presents the stimuli on a computer monitor and separates the ray paths of the two eyes by means of special spectacles that obscure vision in one eye for fractions of a second while a stimulus is presented.

Every now and then ophthalmologists are confronted with patients complaining of a functional visual loss for which no ready explanation can be found in their ophthalmological or neurological condition. When even the most thorough examination and questioning does not reveal a plausible cause of the loss or its reported severity, the ophthalmologist may eventually suspect ocular malingering. Of course the complaint must be considered to be true until proof to the contrary is obtained. Proof of ocular malingering, however, if possible at all, is often extremely difficult and time consuming.

Over the years a number of 'tricks' and special tests have been accumulated to help in the clarification of suspected cases of malingering.¹⁻⁶ Here, we present three new techniques that have proved helpful in our clinic. The first technique is loosely based on the 'preferential looking' method designed several years ago to assess visual acuity in infants.⁷ The second technique uses polarising filters to separate the stimuli to each eye, and flashed presentations to circumvent artefacts caused by eye blinking. The third technique is a modification of the second, using a personal computer and a pair of special spectacles which allow occlusion of each eye separately for fractions of a second.

Material and methods

PREFERENTIAL LOOKING

The first technique uses acuity cards normally used

for assessing visual acuity in infants.^{8,9} The cards are rectangular pieces of grey cardboard (C. 30×60 cm) containing two circular targets of 9.5 cm diameter to the right and left of a small central peephole (Fig. 1). One of the targets is a grating pattern of vertical black-and-white stripes, with different stripe widths on different cards; the other appears uniformly grey but is actually made up of an extremely fine grating beyond the resolution limit of normal adults. The two targets are closely matched in colour and luminance.

For use with adult patients an additional circular coloured target of 7.5 cm diameter is placed in the centre of the card. The cards are presented at eye level through a horizontal opening (20×46 cm) in a grey metal screen (70×170 cm), with the grating target sometimes on the left and sometimes on the right side of the card. The examiner stands behind the screen while presenting the cards and can observe the patient through the peephole in the centre of the card. The patient sits at a distance of 1 m in front of the screen. At this distance the colour target subtends 4.2° and the black-and-white targets 5.4° with a centre-to-centre separation of 14°. The stripe width of the gratings varies from 66 to 0.5 minutes of arc in half-octave steps (equivalent to 20/1300 to 20/10 visual acuity; one octave is a doubling—or halving—of stripe width). Illumination is supplied by overhead incandescent lighting, producing a luminance around 30 cd/m² on the screen.

The patients are told they will undergo a colour vision test and that the perceived brightness of the colour is influenced by the patterns next to it. They are then asked to report the colour of the fixation target, which differs between cards, as well as the

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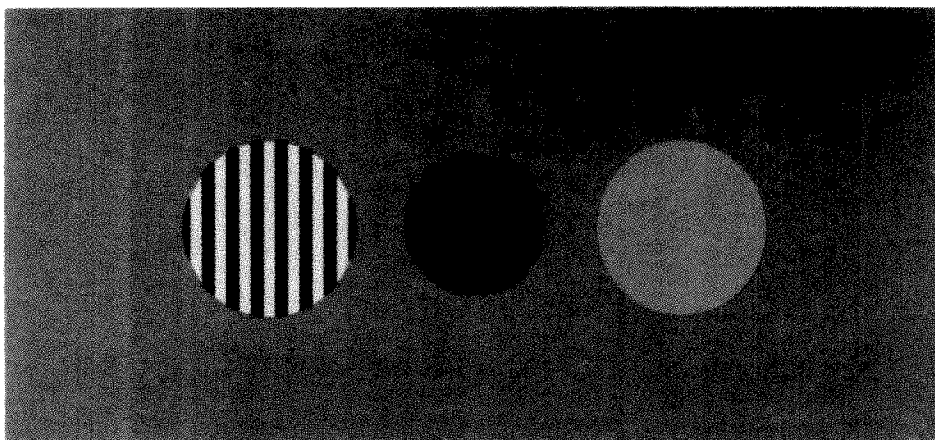


Fig. 1 Example of an acuity card with three circular targets. In this case the right target is uniformly grey, the left one shows a vertical grating pattern, and the middle one consists of a coloured spot. The grating and blank target are of equal mean luminance. A central small peep-hole is shown in the middle target.

position of the grating stimulus. The examiner, who takes care not to note the position of the grating target before presenting a card, then either verifies the patient's verbal report or makes a judgment of grating position on the basis of the patient's fixation pattern, since patients often look longer at the grating than at the uniformly grey target even when they report not seeing the stripes. By presenting gratings of different stripe widths the visual acuity is determined as the finest stripe width reported to be seen or, as in infants, as the finest grating for which the patient shows a fixation preference—assuming that as long as the grating target is preferentially fixated it is also resolved. Until now, no patient has realised that assessment of visual acuity rather than colour vision was the real aim of the examination.

FLASH ACUITY

For the second technique we used a standard Optotype projector equipped with three pieces of Polaroid mounted in front of the objective in a rotatable wheel. The investigator can switch between the filters, which are orientated so that two of them polarise light at right angles to each other, while the third is orientated between the other two. The light source of the projector consists either of the standard 20 W halogen bulb, providing a stimulus luminance of about 30 cd/m², or a commercially available flash gun (60 W). To facilitate the change between the two light sources they were mounted on a sliding adaptor which could be moved easily to bring one of the two sources into place.

The test stimuli are E-hooks—that is, the capital letter E presented in one of four different orientations with the three short lines to the right or left or

above or below the connecting line. These were chosen because, as with Landolt Cs, a 'new' stimulus of a given test size can be produced simply by rotating the one symbol, whereas several templates of each size would be required if different letters or numbers were used. The stimuli are presented singly, as the patients have to know exactly where the stimulus will appear during the very brief presentations, which are far too short for fixation eye movements (below 1 ms).

The stimuli are projected on to an aluminised screen to ensure preservation of the plane of polarisation. The patient's head is stabilised by means of a head rest equipped with polarising filters matched to the two perpendicularly orientated filters in front of the projector. Thus the test stimuli can be flashed to both eyes or to either eye alone without the patient's being aware of which is the case. Further, tilting of the head does not diminish the separation between the ray paths of both eyes, as would have been the case with spectacles worn by the patient.

Incomplete separation of the stimuli of the two eyes by the polarising filters is another problem, common to all polarising tests. To overcome this problem we used polarising filters with very high extinction (99.97%) in combination with a relatively high ambient luminance (20 cd/m²). At the contrasts used, which were not far above threshold in the tested eye, the further reduction in mean luminance for the blocked eye led to strongly decreased resolution thresholds in this eye. Nevertheless, it is difficult to achieve an acuity decrease of more than one log unit in the blocked compared with the non-blocked condition. However, spurious identification of the stimulus through the blocked eye proved not to be a

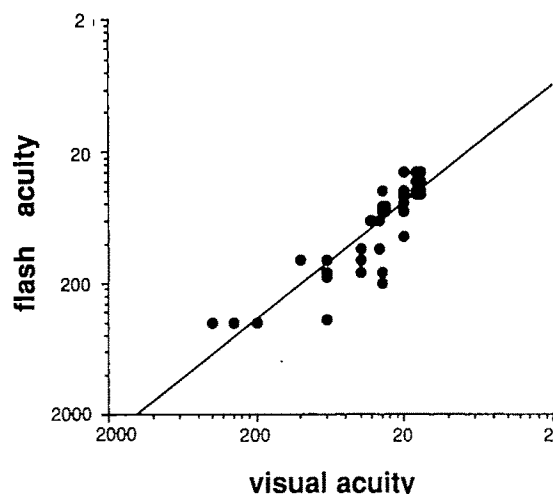


Fig. 2 Relation of flash acuity and standard two-point acuity in our set-up. Acuity is expressed as a dimensionless number (as in 6/6 or 20/20) where the number gives the numerator of the fraction while the denominator is always 20—for example, 20 corresponds to 20/20. Results are from 15 normal observers and 10 patients with different affections of the eye but without a history of malingering: cataract (four cases), glaucoma (three), keratoplastic (two), amblyopia (one). The regression line through the data is given by $0.4 x^{0.9}$; $r^2=0.77$.

serious problem, as we also attempted to reduce acuity in the better eye by addition of spherical lenses (positive dioptres).

The rationale is twofold: firstly, to prevent a stimulus presented to the affected eye from being recognised by the blocked, better eye owing to incomplete extinction. Secondly, this procedure makes the ease of recognition in both eyes similar by blurring the better eye in subjects with distinct interocular acuity differences. Thus the patients are deprived—at least partly—of an easy cue to discrimination between presentations to the better or the affected eye.

FLASH ACUITY WITH A MONITOR

The third technique is a more up-to-date version of the second. Here, a monitor under computer control (Atari ST) is used to present the stimuli, which could be of very different sizes, shapes, and orientations. Usually, E hooks are used, which are presented for a typical duration of 57 ms (4 frames). The patient wears a commercially available pair of spectacles designed for 3-D computer graphics, which are darkened for about 85 ms for one eye by trigger impulses from the computer while the test stimulus is presented. Alternatively, the eyes can be obscured alternately at a frequency of 35 Hz at counterphase so

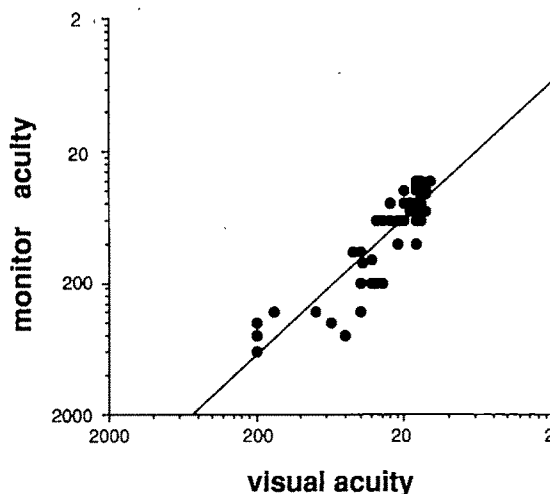


Fig. 3 Relation of monitor acuity and standard acuity in 16 normal observers and 11 patients. The patients suffered from cataract (four cases), glaucoma (two), diabetic retinopathy (one), keratoconus (one), perforating scleral injury (one), injury or herpes simplex of the cornea (two). The regression line is given by $0.3 x^{1.0}$; $r^2=0.81$.

that each eye sees 35 frames per second. Then a stimulus can be shown to one eye for just one frame. Hence only one eye sees the stimulus, without the patient knowing which eye it was. With this method blocking was clearly better than with the polarising filters, resulting in an acuity decrease of the blocked eye by more than a factor of 70. This means that even the largest stimulus cannot be identified through the blocked eye even if it has normal acuity.

The computer receives feedback about the patient's response by means of a joystick that is moved into a position according to the orientation of the E hook—either by the patient or by the investigator. According to whether the response is correct or not, the computer program then chooses the next stimulus size following a staircase procedure. Orientation is varied randomly and thresholds are calculated by probit analysis.

Results and Discussion

The first two of the above techniques have been used over the last year on a number of patients suspected of having better acuities than they were willing to admit. In some of them the results of our three tests proved the initial suspicion to be correct. In applying the tests, however, we also became aware of several shortcomings and limitations of the techniques. Firstly, the two flash acuity tests are not useful if both eyes are reported to have low visual acuity. Moreover, acuity is clearly lower with flash presentation

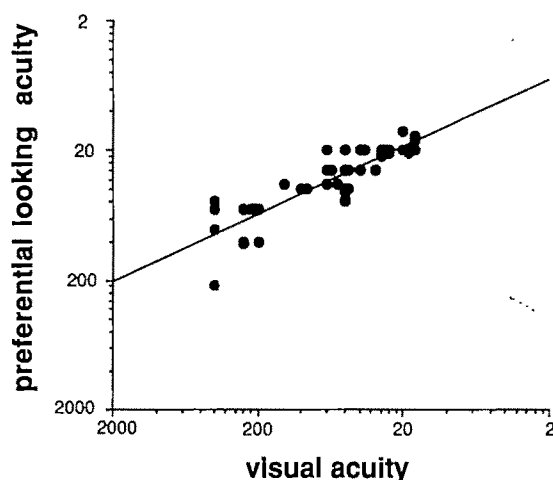


Fig. 4 Relation of preferential-looking acuity and standard acuity. Results of three normal observers and 23 patients. In some of the patients only one eye could be tested. The affections of the patients include cataract (11 cases), glaucoma (one), neuritis of the optic tract (one), pterygium (two), and amblyopia (one) as well as a tumour of the lid (one). The regression line is given by $1.1 x^{0.77}$; $r^2=0.77$.

than with the much longer presentation times used in standard visual acuity testing. We therefore determined norm values for subjects with normal and degraded visual acuity (Figs. 2, 3). The results show that acuities measured by the flash acuity tests and standard acuity testing are closely correlated, making it possible to calculate standard visual acuity from the results of the flash acuity tests. The correlation coefficient (r) for the comparison between flash acuity and standard acuity is 0.88. The correlation between monitor acuity and standard acuity is even closer ($r=0.9$). Both correlations are significant beyond the 0.1% range.

As to the preferential-looking method, this tends to fail if complete blindness is reported, as in the flash acuity test. But in general this technique has also proved to be valuable, and standard acuity can be inferred from the results obtained in normal subjects and in patients without a suspicion of malingering (Fig. 4). Again, the correlation between standard acuity and preferential looking acuity is highly significant, with a correlation coefficient of $r=0.88$.

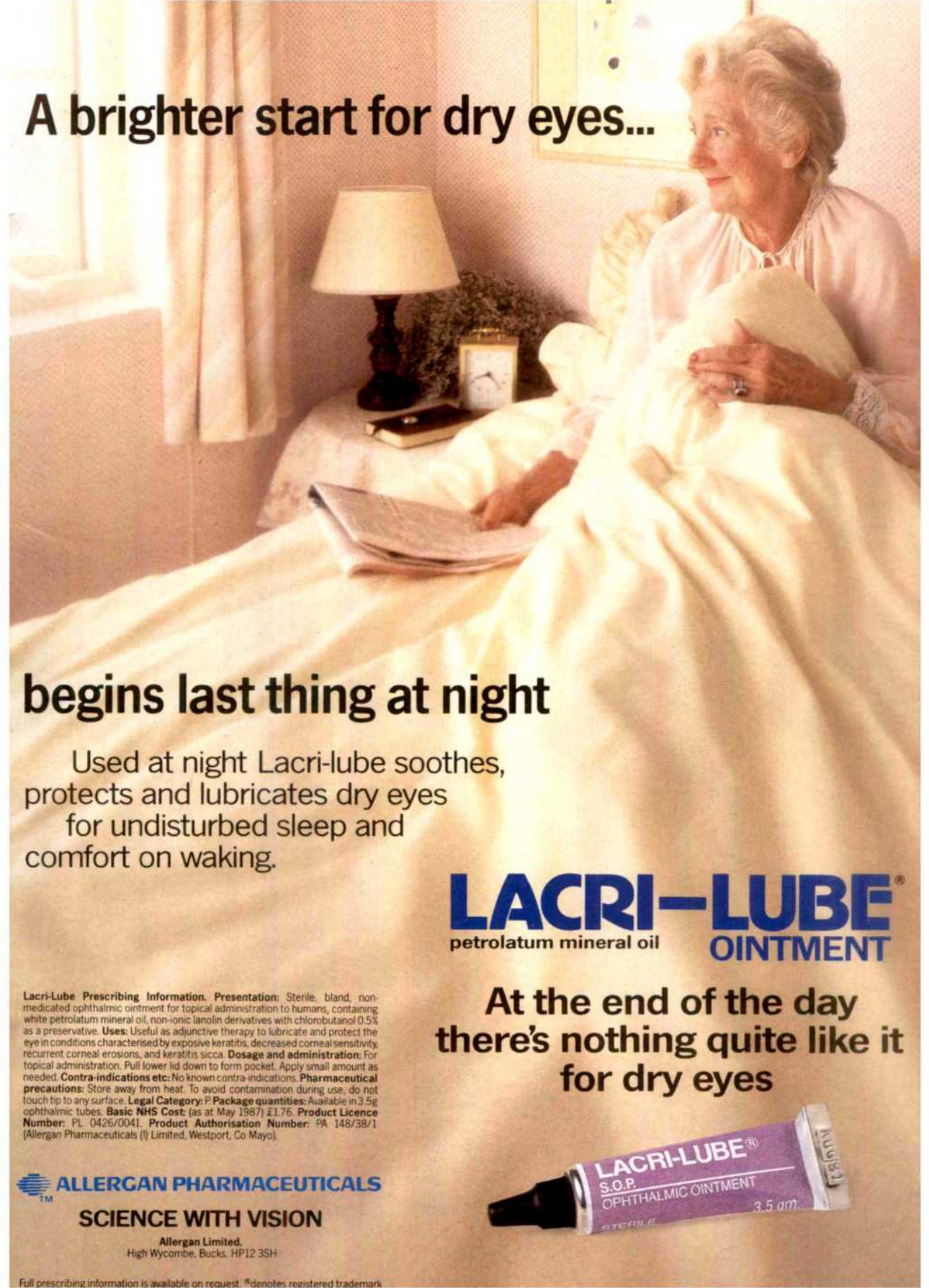
In summary, despite some limitations, the three new techniques described here for the evaluation of visual acuity in uncooperative patients have proved to be successful tools in cases of suspected malingering.

This work was supported by DFG grants Fa 119/3-1 and Fa 119/5-1 to MF and Fa 119/4-2 to GM. We thank H Weller for technical and secretarial help and M Repnow for writing the computer program.

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Convulsion following intravenous fluorescein angiography

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SUMMARY Tonic-clonic seizures followed intravenous fluorescein injection for fundus angiography in a 47-year-old male. Despite precautions this adverse reaction recurred on re-exposure to intravenous fluorescein.

Fundus fluorescein angiography (FFA) is a well established technique in ophthalmic practice. Sodium fluorescein 5 to 10 ml is given by intravenous injection in concentrations of 5 to 25%. Mild adverse reactions are common; severe adverse reactions are exceptional.

We report a unique case of grand mal seizures following intravenous fluorescein.

Case report

A 47-year-old male with axial myopia and myopic chorioretinal degeneration developed reduction of left central vision. The visual acuity was 6/6 Snellen right and 1/60 left. A fresh left macular haemorrhage was present. The patient was otherwise well.

He had been investigated six years previously for left sided paraesthesia, and neurological examination with cranial computed tomography gave normal results. Twenty years ago brief episodes of loss of consciousness had occurred, at which time investigations, including electroencephalography gave normal results. There was no history of anticonvulsant treatment.

Sodium fluorescein, 5 ml of 25% solution, prepared at a local hospital pharmacy was injected intravenously for angiography after the pupils were dilated with 10% phenylephrine and 1% cyclopentolate eyedrops. No immediate adverse events occurred, but headache was experienced one hour later. Two hours after the fluorescein injection, while returning home, generalised tonic-clonic seizures with incontinence occurred. Prompt examination by his general practitioner gave normal results. A

neurological consultation, cranial computed tomography, and digital subtraction intravenous angiography of the cerebral circulation also gave normal results. No adverse reaction to intravenous contrast medium injection occurred. The results of electroencephalography were normal apart from occasional θ activity in the right temporal region on hyperventilation. An untreatable subretinal neovascular zone was demonstrated on the fluorescein angiogram.

Four months later similar events occurred in the right eye. The acuity was now 1/60 right and left. Further fluorescein angiography was requested. Clobazam 10 mg was given orally one hour prior to angiography, which was followed by bed rest under nursing observation. Headache occurred after the angiogram. Ninety minutes after the angiogram generalised tonic-clonic seizures occurred, with loss of consciousness. This brief episode resolved spontaneously. At present he remains otherwise well.

Discussion

Mild adverse reactions to intravenous fluorescein such as nausea and vomiting occur frequently. Severe adverse reactions which involve the respiratory, cardiac, or neurological systems are very unusual. The Fluorescein Angiography Complication Survey, a postal survey of adverse reactions to intravenous fluorescein, estimated tonic-clonic seizures to occur in 1:13 900 angiograms; clinical details were not given.¹ Seizures following intrathecal sodium fluorescein have been reported.² Topical fluorescein eyedrops have also caused generalised tonic-clonic seizures.³ While we are unaware of any other published reports of convulsions after FFA, one other

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case wherein this type of adverse reaction occurred has been reported to the Committee on Safety of Medicines (CSM, personal communication).

There is little doubt that the convulsion in our patient was precipitated by FFA as it happened within two hours of the injection and followed re-exposure to a subsequent batch of fluorescein. This reaction appears to be an idiosyncratic reaction to the 25% sodium fluorescein injection. It is unlikely that the mydriatic eyedrops used were responsible, as they were used uneventfully on other occasions in this patient. As the convulsions occurred 1½–2 hours after the injection, reaction to a metabolite is probable. Drug induced seizures are unusual, occurring in 1·3 per 1000 medical inpatients.⁴

Prophylaxis of this rare reaction is difficult. Pre-medication with a short acting anticonvulsant and subsequent bed rest failed to prevent a seizure

from recurring. Fluorescein angiography in patients known to have had previous seizures should be assessed cautiously. Postangiogram observation may be prudent in such patients. Headache following fluorescein angiography may herald a convulsion.

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Corneal dioptric power after penetrating keratoplasty

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SUMMARY The dioptric power of the cornea (spherical equivalent) was studied in 60 eyes operated on for penetrating keratoplasty. In order to determine the possible influence of (1) the underlying pathology, (2) the presence of neovascularisation, or (3) the size of the graft the sample was divided into four groups, with the following results: group A (keratoconus, same-sized graft)=42.25 D; group B (keratoconus, oversized graft)=45.16 D; group C (keratopathy with minimal or no vascularisation)=45.34 D; group D (keratopathy with significant vascularisation)=45.36 D. The results showed that donor-receptor disparity is the main factor determining the outcome of the postoperative corneal spherical power. There was no demonstrable influence from underlying pathology or the presence of vessels in the receptor cornea.

The so-called triple procedure—combined penetrating keratoplasty, extracapsular extraction, and intraocular lens (IOL) implant—has become an increasingly accepted surgical technique, with excellent reported results and the advantage of performing cataract surgery at the time of the keratoplasty.^{1,2} Although the technique involves no serious difficulties, in most cases the aid of a moderate or high spherical and/or cylindrical lens is needed to achieve satisfactory visual acuity.

Postoperative astigmatism has been widely studied and recently reviewed.³ The spherical defect after the triple procedure is higher than two dioptres in 33 to 74% of the cases, depending on the series, and errors greater than 10 dioptres have been found.⁴⁻⁸

Difficulties in obtaining a minimal spherical error lie in the impossibility of determining the final corneal power (K value) before surgery is performed, provided that the implant power calculation formulas include this parameter.⁹ In such cases surgeons have used a standard IOL or have taken values from the recipient or the fellow eye or from the mean of previous keratoplasties.⁴⁻⁸ However, although it is possible to assess the axial length of the eye, surgical technique will determine to some extent the K values of the grafted cornea.^{10,11} Other factors such as the previous K value, the age of the donor, and pathological changes in the host cornea (vessels, thinning) might also contribute to the final dioptric defect.

The purpose of this study is to evaluate the

spherical equivalent of the K reading from grafted corneas and to consider some of the elements that may affect the result—previous pathology, size of the graft, and suture technique.

Material and methods

Clinical records from all patients operated on for penetrating keratoplasty between January 1985 and February 1988 were reviewed. All the operations had been performed by JAD at the Hospital General de Galicia, Spain. A total of 60 eyes from 56 patients were included in the study, with the graft clear for at least six months after surgery. Indications for keratoplasty were as follows (Table 1): Keratoconus (24 eyes=40%), corneal oedema (12 eyes=20%), herpes simplex virus (HSV) keratitis (8 eyes=13.3%),

Table 1 Indications for surgery

Indication	No. of cases (%)
Keratoconus	24 (40.0)
Corneal oedema	12 (20.0)
Pseudophakic	2
Aphakic	4
Fuchs's dystrophy	3
Failed graft	3
Herpes simplex keratitis	8 (13.3)
Interstitial keratitis	5 (8.3)
Perforating injury	4 (6.7)
Corneal opacity	3 (5.0)
Chemical burn	2 (3.3)
Stromal dystrophy	2 (3.3)
Total	60 (98.8)

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interstitial keratitis (5 eyes=8.3%), and others (11 eyes=18.3%).

Preoperative study included, among other data, the degree of corneal vascularisation, interpreted as follows: 0=no vessels, +=fine vessels in less than one quadrant, ++=thick vessels or fine vessels in more than one quadrant, +++=heavy corneal vascularisation. In all cases corneas from adult donors were grafted.

The surgical technique consisted in a manual trephination on a Teflon block (punch) of the donor cornea from the endothelial side, 0.5 mm greater in diameter than the receptor trephination. In only 14 eyes of the keratoconus eyes did we use a same-sized corneal button. Suturing was done with eight interrupted 10/0 nylon plus a running suture with 16 bites in corneas of 0 or + vessels. In eyes with ++ or +++ corneal vessels 16 interrupted sutures (with no running suture) were used. During surgery release of the cornea from the iris synechiae, extracapsular cataract extraction, posterior chamber IOL implantation, anterior vitrectomy, and/or other manoeuvres were performed when indicated. After the knots were buried, gentamicin and triamcinolone were injected subconjunctivally.

Postoperative treatment consisted of topical dexamethasone and gentamicin every two hours during the daytime; in some cases mydriatics were added. Drugs were tapered during the following weeks, the amount depending on the follow-up findings. When possible, control keratometry was started one month after the surgery, and in the following months interrupted sutures were selectively removed, the removal depending on the corneal astigmatism (removal at the steepest axis). A Javal ophthalmometer was used for keratometric measurements.

In this study we did not consider the corneal astigmatic defect, subjective refraction, or visual acuity. The spherical equivalent of the K value was obtained from the mean power of the steepest and flattest curvature axis once postoperatively between the fourth and the twelfth month, with either the running sutures or most of the interrupted sutures in place.

For the statistical study the eyes were divided into four groups: (A) keratoconus with same-sized graft (n=14); (B) keratoconus with oversized graft (n=10); (C) keratopathy with 0 or + vessels (n=24); and (D) keratopathy with ++ or +++ vessels (n=12). The following parameters were evaluated: (1) diameter disparity between corneal button and recipient bed (groups A and B); (2) corneal peripheral rings according to pathology (groups B and C); (3) the presence of vessels (groups C and D); and (4) the varying sizes of the oversized grafts. Thus

group C was divided into three subgroups: 7.5–8.0 mm (n=5), 8.0–8.5 mm (n=11), and 8.5–9.0 mm (n=8).

For all quantitative comparisons Student's *t* test was used.

Results

Dioptric power of the cornea in the 60 eyes studied varied from 40.0 to 49.25 D, mean 44.59 D. Results for the different groups are summarised in Table 2.

In same-sized grafts for keratoconus (group A) the mean corneal dioptric power was 42.25 D (SD 1.13, range 41.25–44.00), while in oversized grafts (group B) the mean power was 45.56 D (SD 1.60, range 43.50–47.75). There was a significant difference ($p<0.001$) between the groups.

Group C (keratopathy with 0 or + vessels) showed a mean corneal spherical power of 45.34 (SD 1.82, range 41.50–48.50). No statistical difference was evident in cases of keratoconus operated upon by the same oversize graft technique as group B.

When significant preoperative vascularisation was present (group D), the mean postoperative corneal power was 45.36 D (SD 2.92, range 40.00–49.25), which was not significantly different from that in group C. However, dispersion in group D was higher than in group C (oversize grafts were also in this group).

Within group C we compared corneas of different diameters, all with a 0.5 mm oversized graft. Thus, for the 7.5–8.0 mm size the mean K values were 45.87 D (SD 1.39, range 44.25–47.00); for the 8.0–8.5 mm size, 45.29 D (SD 1.90, range 42.25–48.50); for the 8.5–9.0 mm size, 45.08 D (SD 2.13, range 45.50–48.00 D). There were no significant differences among the three groups.

Finally, we compared values from 12 normal fellow eyes for which the grafted eye had a mean K value of 45.38 D. Normal eyes had a mean power of 42.43 D, with an individual disparity in comparison with the fellow eye of between 0.25 and 5.50 D.

Table 2 Postoperative spherical equivalent

Group	Dioptres		
	Mean	SD	Range
Group A (KC, same-sized)	42.25	1.13	41.25–44.0
Group B (KC, oversized)	45.16	1.60	43.5–47.75
Group C (no vessels or +)	45.34	1.82	41.5–48.5
7.5–8.0 mm	45.87	1.39	44.25–47.0
8.0–8.5 mm	45.29	1.90	42.25–48.5
8.5–9.0 mm	45.08	2.13	41.5–48.0
Group D (vessels ++ or +++)	45.36	2.13	40.0–49.25

KC=keratoconus.

Discussion

A growing number of penetrating keratoplasties are giving excellent results in terms of corneal transparency owing to substantial technical improvements, better recognition and treatment of complications, and an absolute increase in the number of keratoplasties performed in the last few years. But interest in the anatomical results has been in part displaced by interest in the optical results. In this area postoperative astigmatism has been the subject of numerous studies, since it is still one of the most frequent complications of this operation.³

The problem of postoperative spherical defects has only recently been raised, and always in relation to the triple procedure. In this operation spherical defects could, at least in theory, be minimised. However, only 26 to 67% of the cases achieve 2 or less dioptres of the ideal refraction.⁴⁻⁸ Gabel *et al.*⁶ thought that axial length could be an important factor, but in most cases it can be determined prior to surgery. Corneal curvature seems to be the single most important source of error.^{4,5,7,8} For normal corneas 0.25 D error in keratometric reading corresponds to about the same amount in postoperative refraction, when the IOL power is calculated through the available formulae.⁹

Our results indicated the following: (1) there is no evidence that the previous corneal pathology or the presence of vessels will influence the final dioptric power of the cornea; (2) it is not possible precisely to calculate the IOL power to achieve an ideal refractive status; (3) when the graft is 0.5 mm larger than the recipient bed, the eye shifts to myopia, while when a same-sized button is grafted the K values are similar to standards; and (4) the final dioptric corneal power does not seem to be influenced by the suture technique.

It is therefore unreliable to use standard or fellow eye K values to calculate the IOL dioptric power in the triple procedure. The highest rates of refractive success have been reported by Binder⁷ and by Musch and Meyer,⁸ with 57 and 67% of their respective patients in the range of ± 2 D of emmetropia. These authors based the IOL power calculation of K values of previous grafts performed with a similar technique. Similarly, three groups have reported keratometric results after penetrating keratoplasty.^{7,8,11} Although they did not specify recipient corneal characteristics, for oversized grafts the three groups found a postoperative corneal power of 45.89 D, 45.4 D, and 45.69 D, respectively. Since our equivalent result was 45.34 D, it seems reasonable to use a 45.5 D K value in the IOL power calculation for the triple procedure. The first of the studies mentioned used a 0.75 mm oversized button and achieved the highest

dioptric power.⁷ Oversized grafts are widely used because of the reduced incidence of glaucoma and wound leaks. In addition trephination from the endothelial face provides a corneal button which is smaller than the diameter of the trephine.¹²

For same-sized grafts a recent study reported a mean K value of 42.98 D,¹¹ while in our study it was 42.25 D. For the IOL formulae standard or 42.5 D K values could be used.

Apart from other problems posed by previously vascularised corneas, they show a wide range of dioptric power in the postoperative period. This could be attributed to the special characteristics of the wound healing process. We can therefore assume that predictability for the final refractive outcome is less accurate for this group of eyes.

Our study did not take into account the presence or absence of an IOL implanted. Keratometry is not supposed to change in the presence of a posterior chamber lens.¹³ An anterior chamber IOL can alter the K values but is not indicated in the triple procedure, even in the absence of the posterior lens capsule.¹⁴ Similarly, when sutures are removed or when a surgical procedure is performed to reduce an eventual astigmatism, it is unlikely that the corneal dioptric power will be modified in terms of spherical equivalent.^{15,16}

In summary, the most important variable in determining the final corneal spherical power after a penetrating keratoplasty is the disparity between the corneal button and the receptor bed size. It must be pointed out that this is also of relevance to regular keratoplasties, since the residual anisometropia can cause visual disturbances which transform a successful operation into a new problem for both the surgeon and the patient. Myopic shift in oversized grafts for keratoconus has been described as an undesirable effect of surgery.¹⁷ Biometry is thus recommended before performing any penetrating keratoplasty to obtain some valuable data for the refractive prognosis. Possibly by changing the relationship between corneal button and receptor bed size we can achieve a refractive status of the eye close to the ideal one.

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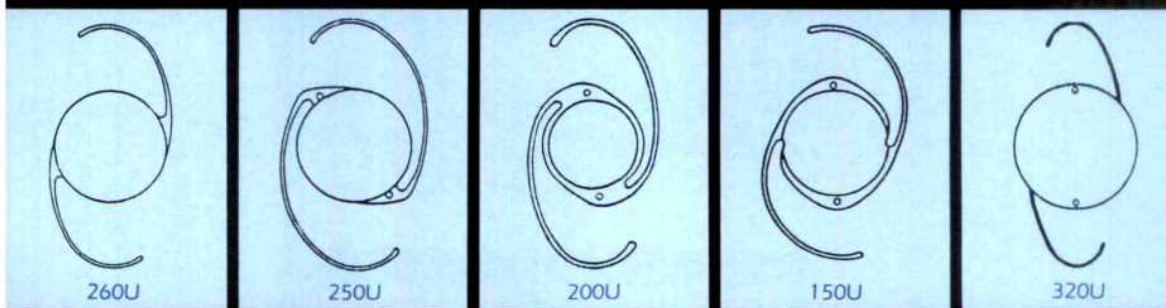
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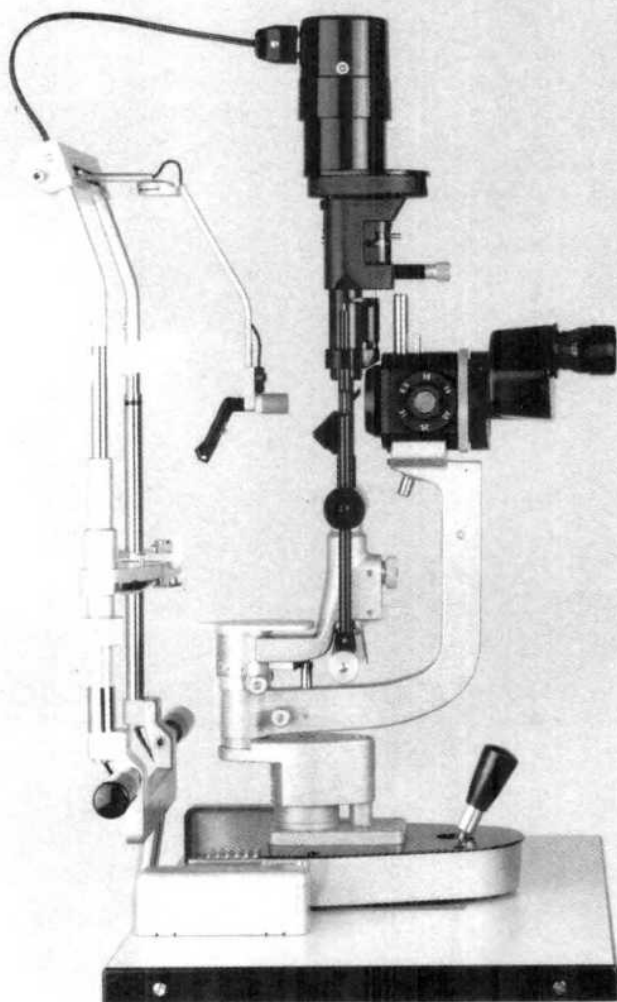
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Primary gelatinous drop-like keratopathy

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SUMMARY This paper describes three siblings, the only affected members of the family, with gelatinous drop-like keratopathy. This rare form of primary corneal amyloidosis has been reported almost exclusively in Japanese literature, and to our knowledge this is the first report of the condition seen in the United Kingdom. Clinical and histological details are presented. The nature and possible aetiology of the amyloid deposits are discussed and the literature is fully reviewed.

The family described here came originally from Teheran and consisted of four siblings whose parents were first cousins. Two of the three boys and the only girl were affected, but no other members of the family or their relatives had a history of eye disease.

The clinical presentation in the three patients was strikingly similar. In each of the three children visual difficulties had begun at the age of 6 years and they had become virtually blind within the ensuing 10 years. There was also extreme photophobia and a characteristic tendency to sneeze violently and repeatedly on exposure to light. There appeared to have been no other history of eye disease or trauma. All three siblings had had a corneal graft in 1981, the oldest boy at that time being 20, his brother 12, and his sister 17. Full clinical details are not available, but 'failure' was said to have occurred after two years in the case of the young men and after only two months in the case of the girl.

At the time of presentation in 1986 the older brother was aged 26, the younger 18, and their sister 24. The clinical features in all six eyes were very similar, but examination was extremely difficult (even under local anaesthesia) because of the intense photophobia. Vision was reduced to barely navigational levels. Both the grafted and non-grafted corneae were opaque, with confluent jelly-like nodules extending throughout, and superficial vascularisation (Fig. 1). The grafted eye in the girl was more opaque than the other eye and was therefore regrafted; in the two men the converse was the case.

All three siblings underwent penetrating keratoplasty. The operations were uneventful except that it was considered helpful to excise the peripheral

nodules in the host anterior stroma to reduce the gross corneal thickness (which was approximately twice normal) to a manageable level. There was a striking early improvement not only in vision but also in the disabling photophobia that existed preoperatively, in spite of one eye still being involved with the keratopathy in each patient.

Two of the three excised discs were fixed in formol saline and examined histologically.

Histology

Microscopic examination of the two corneal discs disclosed areas of irregular epithelial hyperplasia, areas of epithelial atrophy, epithelial oedema, destruction of Bowman's layer, stromal fibrosis, stromal vascularisation and large, mainly superficial, deposits of hyaline, eosinophilic material that gave

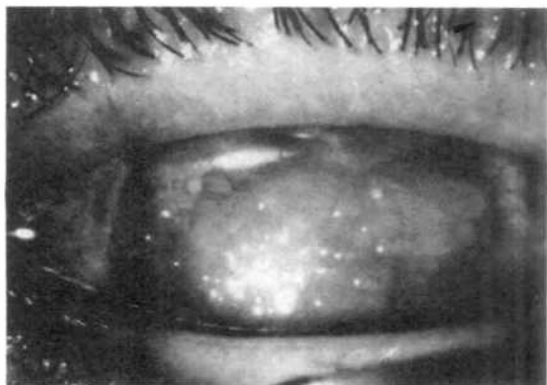
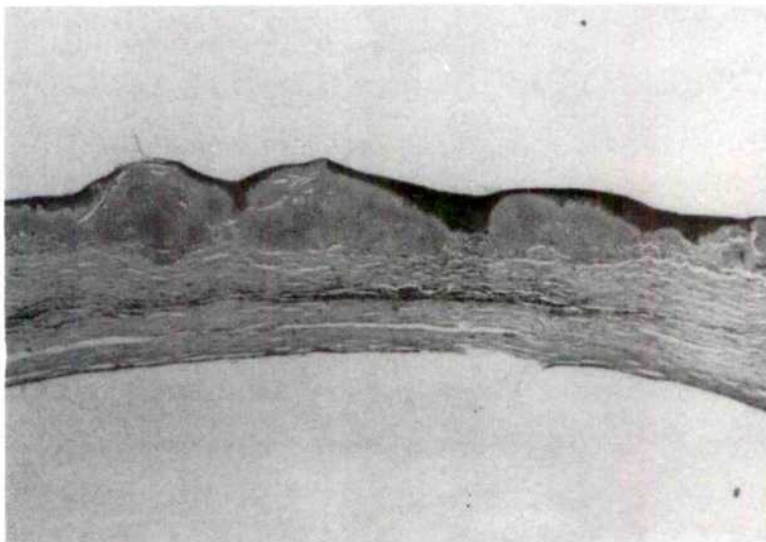


Fig. 1 Preoperative appearance of gelatinous drop-like keratopathy (the sister).

Fig. 2 Corneal disc from the sister showing epithelial atrophy, epithelial hyperplasia, and the considerable extent of the subepithelial and superficial stromal deposits of hyaline material. (Haematoxylin and eosin, $\times 90$).



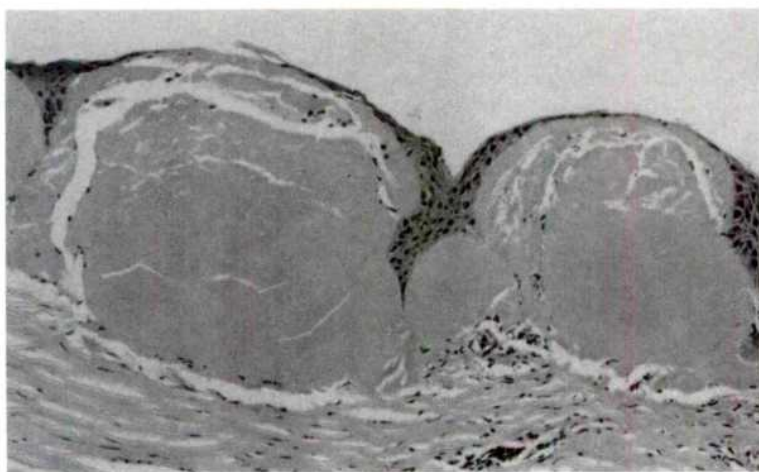
the reactions of amyloid, namely, positive staining with the periodic acid Schiff and Congo red methods, orange-green dichroism with Congo red when examined in polarised light, and bright greenish yellow fluorescence with thioflavin T. In the second of the discs examined (the brother) the eosinophilic deposits penetrated as deeply as two-thirds of the corneal thickness. There was evidence of the previous corneal graft in the first disc examined, and Descemet's membrane and associated endothelial cells were clearly visible in both cases. Electron microscopy in the second specimen revealed fibrils that measured 10 nm in diameter and were consistent with amyloid. The morphological findings in both patients were considered to be compatible with the diagnosis of primary gelatinous drop-like corneal dystrophy (Figs. 2, 3).

Discussion

Primary gelatinous drop-like dystrophy is a rare form of primary familial corneal amyloidosis first described in Japan by Nakaizumi in 1914.¹ About 60 cases have been reported in the Japanese literature since then,¹⁻²¹ and various names have been given to the condition, such as diffuse gelatinous punctate keratitis,² gelatinous drop-like corneal dystrophy,³ familial diffuse gelatinous drop-like corneal dystrophy,⁴ and colloid drop-shaped familial degeneration of the cornea.⁵

Outside Japan reports of the condition are extremely rare, the first being that by Lewkojewa writing from the Helmholtz Institute in Moscow.²² Since then only a handful of clearly indisputable occidental cases of gelatinous drop-like dystrophy

Fig. 3 Higher power view of subepithelial accumulations of hyaline material with atrophy of the overlying epithelium. It is this type of morphology that produces the gelatinous drop-like appearance seen clinically. (Haematoxylin and eosin, $\times 195$).



have been reported, including three cases from the USA,^{23,25} one from Switzerland,²⁶ and one from France.²⁷ In the Swiss case, the patient was a 12-year-old Tunisian boy, and no family history was found. Other reports of proved corneal amyloidosis with appearances similar to gelatinous drop-like dystrophy seem to have been *secondary to pre-existing disease*. Stafford and Fine²⁸ reported on an 11-year-old girl in whom an eye that was enucleated because of retrolental fibroplasia was found to have gelatinous drop-like amyloid deposits. McPherson *et al.*²⁹ reported similar bilateral corneal changes in a 20-year-old Negress and included four further case reports of similar changes, concluding that all were due to pre-existing chronic corneal disease. Interestingly, they went on to examine 200 eyes submitted for pathological examination for other reasons and found that 3.5% had corneal amyloidosis which had not been apparent prior to removal. Similarly Garner³⁰ reported five cases of corneal amyloidosis related to previous corneal pathology. Two of these were related to trauma, one to trichiasis and senescent change, one was found to be lattice dystrophy, and the fifth had an atypical sub-epithelial fibrous plaque. Kanai and Kaufman²⁵ likewise reported on a patient who developed gelatinous drop-like amyloid following primary band-shaped keratopathy. The amyloid was not found histologically in the first specimen but was present two years later in the subsequent corneal disc. One of two North African patients presented by Pouliquen *et al.*²⁷ developed gelatinous drop-like keratopathy after long-standing trachoma, while the other appeared to be a case of primary gelatinous amyloid.

Parents of affected patients are rarely affected, and the inheritance of the condition is regarded as being autosomal recessive with a low degree of penetrance.^{13,14} The clinical manifestations usually begin between the ages of 8 and 18 and initially consist of photophobia, lacrimation, redness, a sensation of grittiness, and intermittently blurred vision. On examination of the cornea numerous small subepithelial gelatinous excrescences are seen across the corneal surface, giving the whole an appearance variously described as 'mulberry like' or 'toad skin' like. In advanced cases (often before age 20), the symptoms are very severe, with profound photophobia and visual loss. At this stage there may be stromal neovascularisation. No systemic associations have been reported.

It was not possible, with such advanced cases as ours, to comment on the possible origin of the amyloid fibrils other than to state that the histology suggested that the major site of deposition was anterior stroma with erosion of Bowman's layer. There has been some debate as to the origin of the

amyloid. Hohki *et al.*³⁰ have postulated that it may be produced by both keratocytes (as would appear to be the case with lattice dystrophy³¹) and basal epithelial cells. Nagataki *et al.*¹⁷ consider that the keratocytes are not involved, and along with Ohnishi *et al.*²¹ consider that the basal epithelial cell layers are solely responsible.

Some of the reports discussed above have clouded the issue by describing conditions similar to primary gelatinous drop-like keratopathy, but there is no doubt that this strange and most disabling condition is a discrete entity that can be separated from other forms of familial amyloidosis by the absence of systemic involvement, the unique ocular appearances (which occur early and advance rapidly),³² and the characteristic localisation of the larger amyloid deposits in the superficial cornea.

The precise type of amyloid found in gelatinous drop-like keratopathy has yet to be fully elucidated. Further definition of chemical structure may be possible by immunohistochemical techniques such as those applied by Hida *et al.*³³ to lattice dystrophy types I and II and a newly recognised form, type III. So far attempts at precise chemical description of lattice dystrophy type I by these techniques have produced conflicting results, which are thought³³ to be due to differences in immunohistochemical techniques and the antibodies used or to reflect heterogeneity inherent in type I. Evolution of newer methods applied to unfixed, freshly excised corneae may allow further definition of the amyloid material, including the deposits of gelatinous droplet keratopathy.

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Corneal thickness in nephropathic cystinosis

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SUMMARY Cystinosis is a rare autosomal recessive metabolic disorder in which non-protein cystine accumulates within cellular lysosomes owing to a defect in lysosomal cystine transport. The pathognomonic ocular manifestation of cystinosis is the deposition of distinctive iridescent crystals in the cornea, not associated with any inflammatory response or recognised change in corneal function. We measured corneal thickness in nine patients with infantile nephropathic cystinosis. We also studied a corneal button from one of these patients who underwent corneal transplantation. All nine patients had increased corneal thickness in comparison with an age matched control population. Electron microscopy analysis of the cystinotic button revealed structural changes of both epithelium and endothelium layers. Increased corneal thickness in patients with nephropathic cystinosis may reflect subclinical corneal oedema.

Cystinosis is an autosomal recessive metabolic disorder characterised by the accumulation of non-protein cystine within lysosomes of cells owing to a defect in lysosomal cystine transport.¹ It occurs in three phenotypical forms: a nephropathic childhood form, a benign adult form, and an intermediate adolescent form. The childhood form is the most common and the most devastating. Systemic complications include the renal Fanconi syndrome with rickets and growth retardation, and renal failure that necessitates transplantation by an average age of 10 years.² The adolescent and adult forms are associated with milder disease but share the pathognomonic ocular manifestation of cystinosis: distinctive iridescent crystals in the cornea and conjunctiva.³ The crystals are birefringent, intracellular, and of varying form. Needle shaped or fusiform crystals are seen in the cornea, whereas polymorphous, rectangular, or rhomboidal crystals infiltrate the conjunctiva.^{4,5} Ultrastructural analysis has shown these crystals to be intralysosomal.^{6,7} Crystallographic analysis has shown the rectangular forms to be composed of L-cystine.⁸ Patients with cystinosis commonly complain of photophobia and occasion-

ally develop corneal erosions.⁹ A pigmentary retinopathy affecting the periphery has been described in the nephropathic form of the disease¹⁰ but not in the benign form.¹¹ Crystals are also seen in the iris, ciliary body, choroid, retinal pigment epithelium, sclera, episclera, extraocular muscles, and optic nerve sheath.^{3-5,12}

The formation of corneal cystine crystals has a recognisable spatial as well as temporal sequence.¹³ Anterior deposition begins early in life and proceeds posteriorly as the patient ages; deposition advances more rapidly at the periphery.¹³ We measured corneal thickness in a group of patients with infantile-onset nephropathic cystinosis to determine whether the accumulation of corneal intralysosomal cystine is associated with recognisable changes. We also examined a corneal button from one of our patients undergoing corneal transplantation and correlated its ultrastructure with our clinical observations.

Subjects and methods

We studied nine patients between the ages of 3 and 28 (mean age=12.7 years) with infantile onset nephropathic cystinosis. Three were male and six female. Three were taking oral cysteamine (a free thiol with cystine-depleting capacity). Five of the nine had had successful renal transplantation and three of these

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were taking steroids. The patients had a complete neuro-ophthalmological examination by one of us (BK). All were essentially emmetropic and had abundant crystal deposition in their conjunctiva and cornea. Pupillary responses were normal, without evidence of afferent pupillary defect. Ophthalmoscopic examination revealed mild depigmentation of the peripheral retina in all the patients. The fundus in all of them was patchy and mottled from the mid equator to the ora serrata. The optic nerves were of normal colour, contour, and capillarity. No abnormality of nerve fibre layer could be detected.

A control group consisted of nine normal youngsters without corneal abnormalities or history of ocular disease. Their ages ranged from 3 to 16 years (mean 10.4 years). Four were male and five female. None of the subjects in either group were taking oral contraceptives or wore contact lenses—factors which may cause an increase in corneal thickness.¹⁴

We used a commercially available ultrasonic pachymeter (DGH-2000 Ultrasonic Pachymeter, DGH Technology Inc., Pennsylvania) to determine corneal thickness.¹⁵ The pachymeter has a 1.5 mm diameter solid probe tip and a transducer frequency of 20 mega hertz. The instrument has a measurement range of 0.20 to 1.3 mm, a resolution of 1 μ m, and an accuracy of ± 5 μ m.

All measurements were made by one of us (BK). The pachymeter probe was applied to the centre of the cornea after topical application of 0.5% proxymetacaine (proparacaine). Three measurements were recorded for each eye; the average of the three measurements was calculated and recorded.

We examined a corneal button obtained from patient 8, who (after our study) underwent corneal transplantation at age 20. The button was taken from the operating room and immediately fixed in half-strength Karnovsky's solution (2.5% glutaraldehyde and 2.0% paraformaldehyde in 0.1 M phosphate buffer, pH 7.2). The tissue was processed for transmission electron microscopy by post-fixation in 2.0% osmium tetroxide, and dehydrated through a series of graded concentrations of ethyl alcohol and in propylene oxide. The tissue was embedded in Polybed resin (Polysciences, Warrington, PA). Selected areas were examined by transmission electron microscopy. Sections 1 μ m thick were prepared for light microscopy by toluidine blue staining.

Results

The mean corneal thickness in the patients with cystinosis was 611.2 μ m (n=18, SD=42.4, SE=10.0) (Table 1). The mean corneal thickness of the normal subjects was 548.4 μ m (n=18, SD=28.4, SE=6.7)

Table 1 Corneal thickness in patients with nephropathic cystinosis

Patient no.	Age (years)	Central corneal thickness (μ m)	
		Right eye	Left eye
1	3	623	627
2	4	647	599
3	7	605	573
4	9	628	648
5	9	572	558
6	15	644	647
7	19	562	562
8	20	665	675
9	28	590	549
Mean (SD)	12.7 (8.4)	611.2 (42.4)	

Table 2 Corneal thickness in control group

Patient no.	Age (years)	Central corneal thickness (μ m)	
		Right eye	Left eye
1	3	555	589
2	6	576	575
3	8	552	557
4	9	547	556
5	11	517	504
6	13	559	544
7	13	563	571
8	15	564	558
9	16	494	491
Mean (SD)	10.4 (4.3)	548.4 (28.4)	

(Table 2). Corneal thickness was significantly higher in the cystinosis patients (Student's *t* test, $p < 0.001$). Simple linear regression analysis showed poor correlation of the corneal thickness in cystinosis with patient age ($r = 0.2$).

This increase in corneal thickness was not accompanied by obvious abnormality of epithelium or endothelium, nor was it reflected in decreased acuity or clinically recognisable oedema. It was not accompanied by raised intraocular pressure. No abnormality recognisable at the slit-lamp (other than stromal infiltration with crystalline material) could be seen.

Histological examination of the corneal button revealed an intact epithelium with normal Bowman's layer and Descemet's membrane. Basal cells of the epithelium showed intracellular oedema. Superficial keratocytes showed vacuolated cytoplasm. There was degeneration of the endothelium with focal cell loss. Ultrastructural examination of the cornea showed the presence of rectangular intracytoplasmic crystalline inclusions throughout the entire corneal stroma, within keratocytes. Deposition of crystalline inclusions was not associated with any recognisable inflammatory reaction or change of extracellular

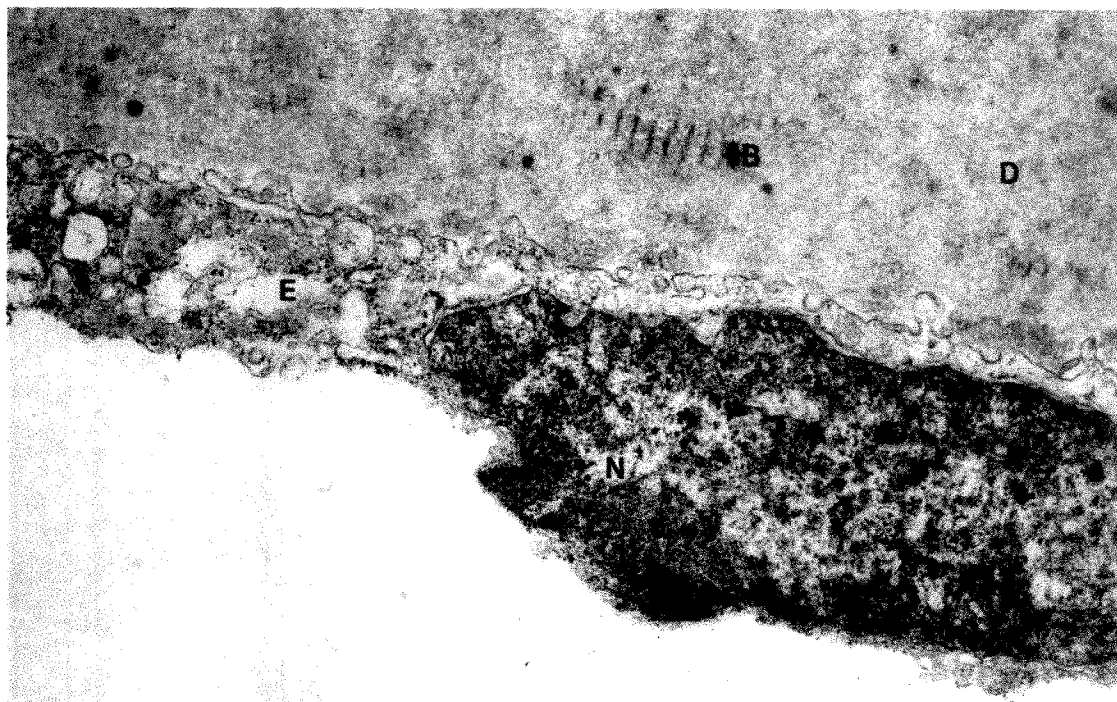


Fig. 1 Electron microscopy of endothelial cell (E) reveals swollen mitochondria with disarray of cytoplasmic organelles. Legend: E=endothelial cell. B (arrow)=banded basement membrane. D=Descemet's membrane. N=nucleus of endothelial cell ($\times 4800$).

matrix. The endothelial cells showed disorganised organelles within their cytoplasm. Mitochondria were swollen and cristae were indistinct (Fig. 1).

Discussion

Corneal thickness varies little either between patients or between eyes of the same patient.¹⁶ The ultrasonic pachymetric determination of corneal thickness used in this study has been shown to be a highly reliable method which eliminates errors due to observer interpretation inherent in the optical measurement of corneal thickness.¹⁷ The mean corneal thickness of our control patients is similar to that found by previous investigators,^{18,19} who reported the average thickness of the normal human cornea (measured centrally) to be between 0.50 and 0.57 mm.

Corneal thickness depends on the water content of the cornea; there is a linear relationship between corneal thickness and hydration.¹⁹ For the human cornea Mishima found the relation between the two measurements to be defined by the equation: $H = 7.0q - 0.64$, where H is the hydration expressed in water weight per dry weight of tissue and q is the

corneal thickness in millimetres.¹⁹ The thickened cystinotic cornea may therefore reflect increased water content.

Absorption of water into the polysaccharide matrix of the cornea leads to increased corneal thickness. Yet the cornea swells only in a direction perpendicular to its plane of curvature, a result of the unique arrangement of collagen fibrils parallel to the plane of the corneal curvature.¹⁹ The expansion of the stroma along this corneal plane is restricted by the planar arrangement of the collagen fibrils; there are few fibrils running in the anterior to posterior direction to restrain swelling.

The maintenance of corneal hydration is dependent on metabolic activity within the corneal endothelium. Ouabain, an inhibitor of Na^+/K^+ -ATPase (an enzyme necessary for active transport), causes corneal swelling when applied directly to endothelium. Oxygen is necessary for the maintenance of corneal hydration,¹⁹ which indicates that the aerobic phase of the carbohydrate metabolism provides energy for the maintenance of the corneal thickness. Langham and Taylor found an inhibitory effect of 2,4 dinitrophenol on the fluid excretion of the cornea²⁰ and concluded that the dehydration of the cornea is

linked to oxidative phosphorylation. Since the corneal endothelium is rich in mitochondria, the site of the electron transport system, it is assumed that the active trichloroacetic acid cycle in the corneal endothelium supplies the energy necessary for the maintenance of normal corneal thickness.

The cornea swells when damaged. Increased corneal thickness may be an early sign of corneal dystrophy, keratitis, or trauma, when each interferes with corneal endothelial function; the degree of swelling generally parallels the severity of the underlying disease.¹⁹ Epithelial damage also results in swelling of the cornea, though it is less pronounced.

Patients with nephropathic cystinosis have excessive amounts of cystine in cellular lysosomes. Cystine is not known to be increased in collagen fibrils of the cornea, but it accumulates within keratocytes and epithelial cells.²¹ An osmotic gradient might result from increased cystine within the corneal stroma and account for some element of increased stromal hydration. The intralysosomal site of cystine deposition, however, would argue against the crystals themselves generating any change in tissue oncotic pressure. We think it more likely that the altered corneal thickness observed in our cystinotic patients is a reflection of subclinical dysfunction of epithelial and/or endothelial cells leading to the occurrence of clinically unrecognised stromal oedema. This hypothesis is supported by the ultrastructural changes we observed in the epithelial and endothelial layers of the cornea in our cystinosis patients. We speculate that increased amounts of cystine interfere with fluid transporting mechanisms of the corneal endothelium and epithelium, leading to altered water content of the cystinotic cornea. There is experimental support for striking similarities between transport related characteristics of the corneal endothelium and the kidney proximal tubule epithelium.²² The alterations of corneal physiology which we believe are caused by epithelial and endothelial dysfunction may be analogous to the disturbances in the proximal tubule epithelium that culminate in the Fanconi syndrome. Interference with active transport across epithelial surfaces may be the mechanism whereby accumulation of cystine causes both the renal Fanconi syndrome and increased water content of the cornea manifest as increased corneal thickness. Whether this shared epithelial anomaly and ensuing increase in corneal thickness occur in association with non-cystinotic causes of the Fanconi syndrome require further study: such studies are now in progress.

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Corneal subepithelial monoclonal kappa IgG deposits in essential cryoglobulinaemia

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SUMMARY A 60-year-old man suffering from photophobia and visual disturbances was found to have bilateral superficial corneal grey-white gelatinous deposits. An abnormal cold-precipitable serum component was found and characterised as homogeneous IgG-kappa immunoglobulin. Corneal immunohistochemical examination revealed subepithelial IgG-kappa deposits, focally replacing Bowman's layer. The patient underwent superficial keratectomy in both eyes with satisfactory visual results.

Bilateral corneal deposits have been described in association with dysproteinaemia since 1934.¹⁻⁸ To our knowledge there is only one report⁹ describing corneal subepithelial immunoglobulin deposits in benign monoclonal gammopathy, simulating the clinical non-crystalline appearance and distribution of the corneal deposits found in our patient. Such deposits have never been described in essential cryoglobulinaemia. We present the results of bilateral superficial keratectomy performed on a patient with essential IgG-kappa cryoglobulinaemia, the only manifestation of which was the superficial corneal immunoglobulin deposits.

Case report

A 60-year-old man presented with photophobia, tearing, and gradually decreasing vision. On examination his best corrected visual acuity (VA) was 6/12 in both eyes. Slit-lamp examination of both corneas showed raised gelatinous grey-white subepithelial avascular nodules, in the corneal periphery but sparing the limbus (Fig. 1). These confluent non-crystalline nodular masses extended towards the visual axis by finger-like projections. The corneal stroma, Descemet's membrane, and endothelium appeared normal. The anterior and posterior seg-

ments were completely normal, as were the eyelids and conjunctiva.

The physical examination and bone x-rays showed nothing abnormal.

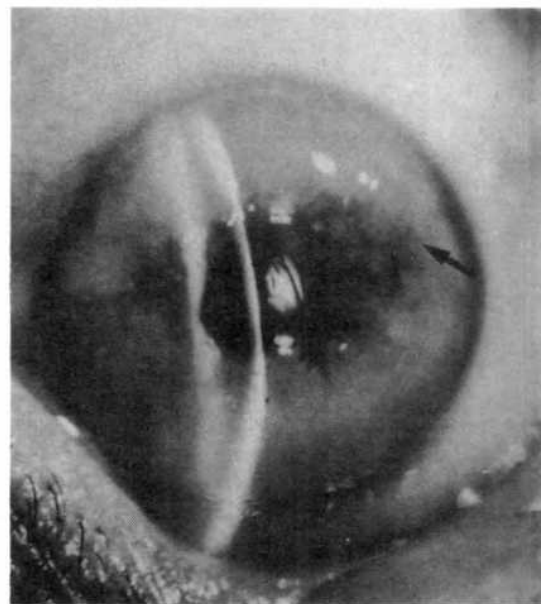
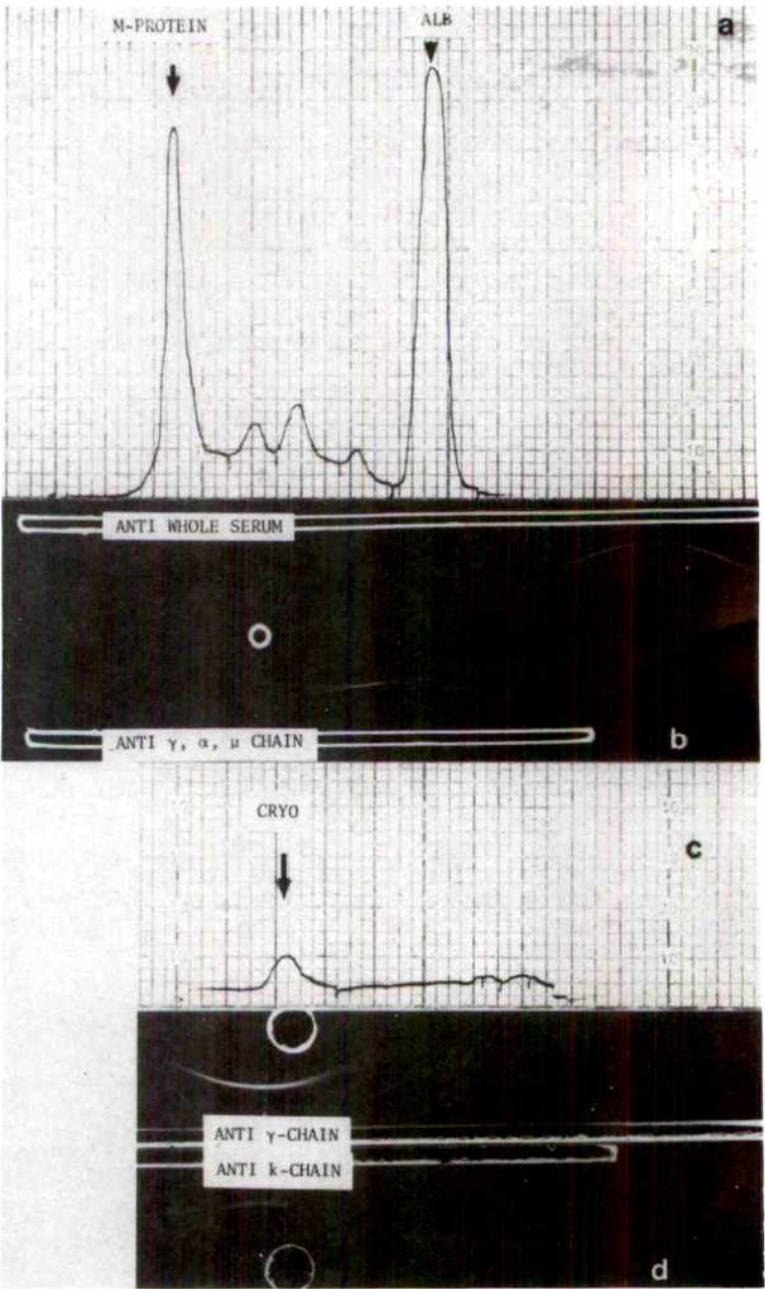


Fig. 1 Slit-lamp photograph showing the confluent nodular gelatinous-like superficial corneal deposits, extending towards the corneal centre by finger-like projections (arrow).

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Fig. 2 (a-d) Electrophoresis and immunoelectrophoresis of the patient's serum (a, b) and cryoprecipitate (c, d), revealing the presence of homogeneous IgG-kappa immunoglobulin



Subsequently the patient's serum was examined. A cryoprecipitate was discovered and was characterised by immunoelectrophoresis as a homogeneous IgG-kappa immunoglobulin (Fig. 2). Serum immunoglobulins were quantitated by nephelometry (Table 1).

Table 1 Results of serum cellulose acetate electrophoresis

Protein	g/l	Normal range g/l
IgG	30	2.0-10.5
IgA	1.86	0.8-2.7
IgM	1.24	0.4-1.1

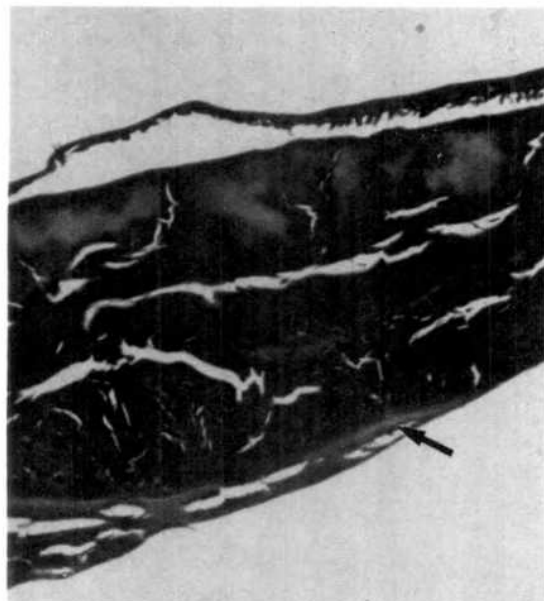


Fig. 3 Massive accumulation of red coloured subepithelial deposits located between the atrophic epithelium and Bowman's zone (arrow), which is focally disrupted. (Masson-trichrome stain, original magnification $\times 250$).

As a bone marrow biopsy showed normal appearances, the diagnosis of essential IgG-kappa cryoglobulinaemia was established.

A small lamellar biopsy was performed in the right cornea. The histopathological examination with haematoxylin-eosin showed eosinophilic subepithelial deposits, located between Bowman's layer or superficial stroma and basal epithelial layer. Bowman's layer was focally disrupted and replaced by the eosinophilic periodic acid Schiff positive material. With Masson trichrome staining red-coloured aggregates were seen beneath the elevated atrophic epithelium (Fig. 3). Stains for amyloid were negative. Electron microscopy revealed that the deposits were composed of numerous rod-shaped bodies (Fig. 4). Each rod was composed of parallel fine filaments with a 9.5–10 nm periodicity (Fig. 5). A conjunctival biopsy revealed the presence of conjunctival subepithelial aggregates of homogeneous kappa-IgG (Fig. 6).

During the following years the VA decreased gradually to 6/40, with J-7 in both eyes. It was not possible to perform skiascopy or keratometry, as the corneal surface was irregular.

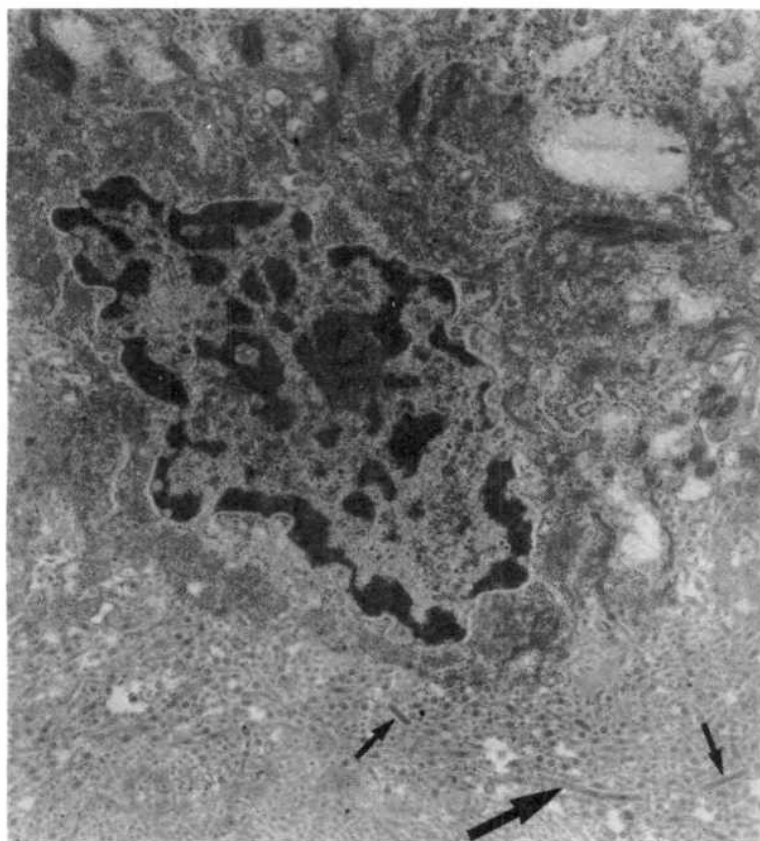
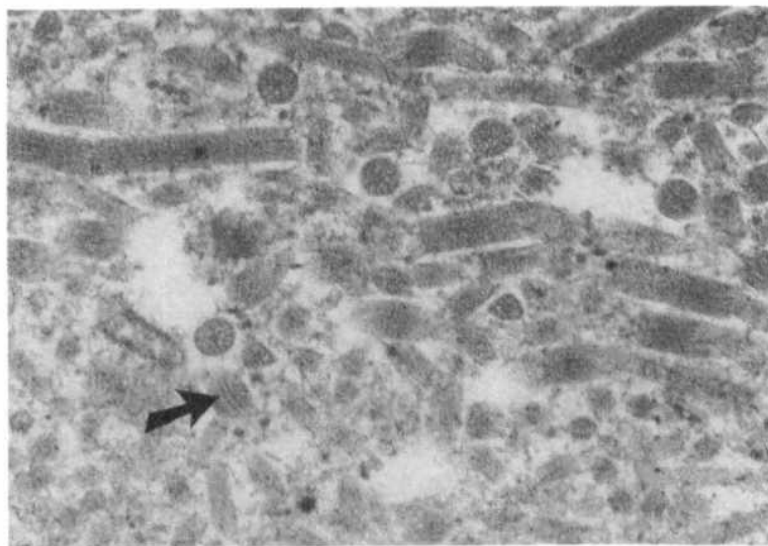


Fig. 4 Electron microscopy of the corneal biopsy specimen showing numerous subepithelial rod-shaped bodies (arrows). (Original magnification $\times 8200$.)

Fig. 5 At higher magnification (EM) the rod-shaped bodies are seen to be composed of parallel fine filaments (arrow) with a periodicity of approximately 10 nm. (Original magnification $\times 42\,000$).



Owing to the subepithelial location of the corneal deposits, approaching the corneal centre, it was decided to perform superficial keratectomy by shaving the cornea with a scalpel blade. After this procedure, the VA improved to 6/7.5 in the right eye and 6/7 in the left, with J-1 in both eyes. The keratometry revealed bilateral regular astigmatism of 0.5 D.

Immunohistochemical examination of the keratectomised material showed that the corneal immunoglobulin deposits were antigenically identical to the homogeneous IgG-kappa (cryoglobulin) serum component.

Fourteen months after the operation the corneal surface was completely smooth, and a peripheral

band of superficial stromal scarring was noted bilaterally (Fig. 7).

Discussion

Corneal immunoglobulin deposits in association with hypergammaglobulinaemia have been described mainly as crystals.^{2,8,10-14} The definitive evidence that the latter corneal crystals are immunoglobulins was provided by Klintworth *et al.*⁶ using immunofluorescent and immunoperoxidase techniques. Garner

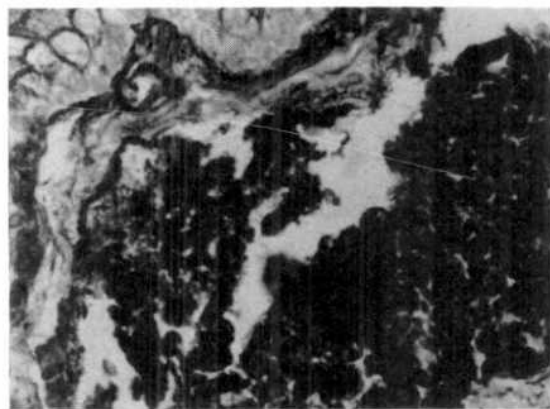


Fig. 6 Massive accumulation of conjunctival subepithelial immunoglobulin G deposits (anti-IgG positive). (Immunoperoxidase stain, original magnification $\times 400$.)

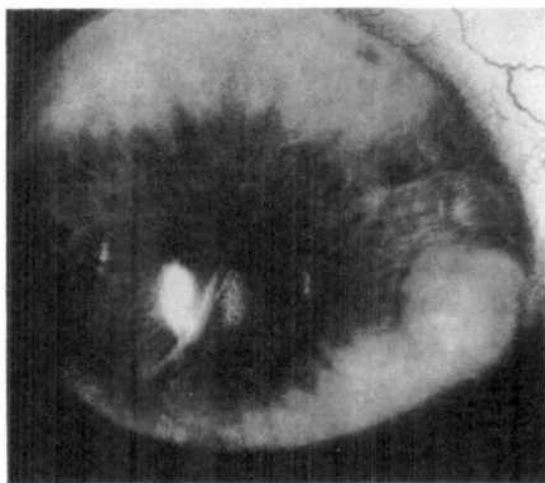


Fig. 7 Patient's right cornea six months after superficial keratectomy, showing confluent superficial stromal opacification covered by a completely smooth epithelium in those areas where the deposits have been removed.

and Kirkness¹⁴ maintain that the unifying characteristic of these crystals is the 10 nm periodicity of their banded infrastructure.

The clinical appearance and anatomical location of these corneal deposits may be quite variable.^{13,14} In most cases they are found in the stroma^{2,5,7-13} and only rarely in the corneal epithelium proper⁴ or immediately beneath it.⁹ Paraproteinaemic keratopathy in association with true monoclonal gammopathy of unknown significance (MGUS) is very rare and has been reported in only four cases.^{4,9,13,15} Our patient is the fifth recorded case with MGUS. However, as the monoclonal paraprotein found in his serum had the characteristics of cryoglobulin his disease may be defined also as essential cryoglobulinaemia.

As regards cryoglobulinaemia, Palm¹⁵ was the first author to report on superficial corneal deposits in a case of crystal cryoglobulinaemia. The nature of these corneal deposits differed from that of our patient in that they had a crystalline appearance. Oglesby¹⁶ is the only author to report on corneal non-crystalline deposits in a patient with cryoglobulinaemia, which was associated with reticulohistiocytosis. The corneal stromal involvement in this patient was predominantly posterior. However, Oglesby¹⁶ presented no histological or immunohistochemical proof for the presence of corneal immunoglobulin deposits. No surgical or medical treatment was mentioned in these two reports.^{15,16}

Allansmith and colleagues^{17,18} reported that almost all immunoglobulins can be found in normal corneas and that their concentration correlates with the serum level. They maintain that corneal immunoglobulins are derived mainly from the serum by diffusion from perilimbal vessels.

The presence of a cold precipitable immunoglobulin in the serum of our patient may explain its massive preferential accumulation in the corneal subepithelial region, as it is probably one of the coldest areas in the human body.¹⁹ According to Waltman and Hart¹⁹ the difference in temperature between the rabbit cornea and the iris amounts to 5°C. As the cryoglobulin precipitates in a temperature below 34°C, it may undergo crystalloid changes following precipitation under the corneal epithelium, the temperature of which is probably around 32°C.

These corneal cryoglobulin precipitates found in our patient were removed by superficial keratectomy, after which a smooth corneal resurfacing was achieved. For the time being invasive surgical techniques, such as perforating or lamellar keratoplasty, have been postponed. Whenever the above-described corneal deposits recur outside the corneal

centre, superficial keratectomy can be repeated. However, if they appear in the central zone, keratoplasty is indicated. It is our opinion that this procedure should probably be supplemented in future either by plasmapheresis or by low dosage chemotherapy²⁰ in order to keep the corneal graft clear.

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Corneal amyloidosis

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SUMMARY A 54-year-old man presented with a corneal lesion which on excision biopsy was found to be composed of amyloid. This material was presumably laid down in response to chronic irritation from the scarred lid and thus represents an example of secondary localised amyloidosis.

A 54-year-old man presented to the outpatients department complaining of a longstanding sore right eye. Thirty years previously he had sustained an injury to the right upper lid in which tissue was lost. The lid had been repaired with a skin graft and the tarsal plate sutured, but the lid had a rounded notch in the margin, with entropion, and the tarsal surface was very uneven owing to bunching and scarring of the tarsal repair. Thus over a period of some 30 years part of the right cornea had been exposed and had undergone constant trauma from the deformed lid. The discomfort had been bearable until two years previously, since when tearing and photophobia had forced him to cover the eye and eventually to seek advice.

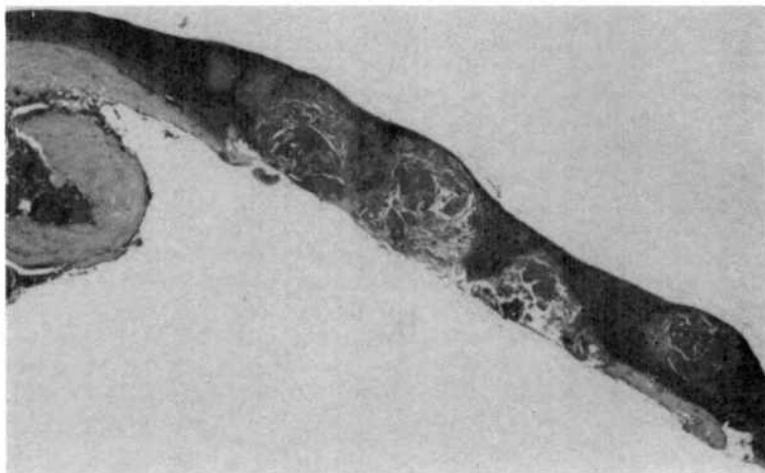
On examination the vision was 6/4 right and 6/6 left. There was a raised vascularised irregular area on

the left cornea close to the limbus at 2 o'clock. This extended towards the centre of the cornea for 3 mm. This raised area corresponded with the upper lid defect.

Excision biopsy of the abnormal limbal and corneal area was performed. The defect was allowed to heal spontaneously. Histological examination showed that this tissue had a normal epithelium with nodular deposits of amyloid in the deeper layers (Figs. 1, 2). It stained red with Congo red and displayed dichroism, that is, a change in colour that varies with the plane of polarised light (Fig. 3). Amyloid is dichroic only to green light.

Later the upper lid deformity was revised with full thickness excision of the scarred section of lid to prevent further irritation of the globe. The lid tissue was sent for histological examination. This showed that the upper lid was scarred throughout its thick-

Fig. 1 Deposits of amyloid in the cornea. (HE $\times 35$.)



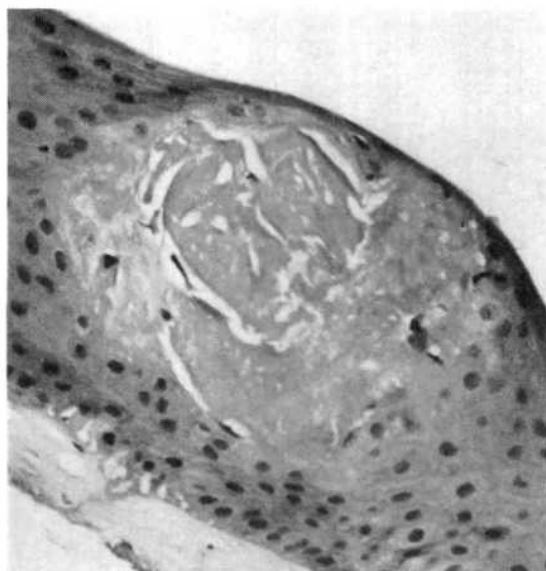


Fig. 2 Higher magnification of amyloid deposit. (HE $\times 210$.)

ness, but there was no evidence of amyloid. Nor was there evidence of amyloid deposition in any other organ of the body, and the patient was otherwise in good health.

Discussion

There are a number of conditions in which amyloid is found in the eye. Yanoff and Fine¹ classify amyloidosis into two main groups, primary and secondary, each of which is subdivided into systemic and local. Systemic primary amyloidosis is sometimes associated with plasmacytic and lymphocytic neoplasia; it shows a distribution of amyloid in the alimentary tract, the cardiopulmonary system, and the skin. The

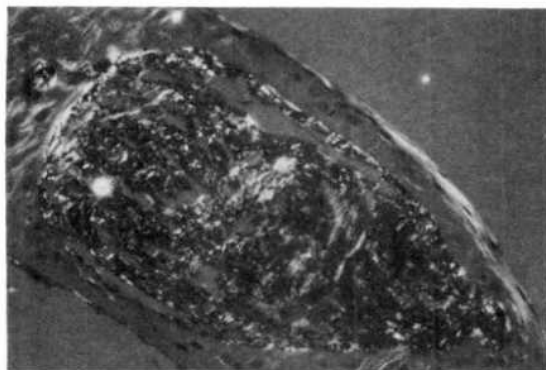


Fig. 3 Staining with Congo red showed apple green colour of amyloid deposit in polarised light. ($\times 145$.)

eye may be involved in a number of ways, the most important being the appearance of vitreous opacities, but ocular palsies, neuroparalytic keratitis, and glaucoma may result from amyloid deposition in the tissues. Amyloid fibrils here consist of fragments of immunoglobulin light chains.²

Localised primary amyloidosis may also be found in the eye in the form of small red nodules in the conjunctiva and lids. The intraocular structures are not involved. Lattice corneal dystrophy, one of the inherited corneal dystrophies, is considered by some to be a form of localised primary amyloidosis of the cornea.

Secondary systemic amyloidosis accompanies some chronic diseases, with amyloid deposits chiefly in the spleen, kidney, and liver. The eyelids may rarely be involved. Secondary amyloid fibrils consist of a non-immunoglobulin-related protein, amyloid A protein.² Secondary localised amyloidosis is a condition in which amyloid is deposited as a result of chronic local inflammation and has been described in both the conjunctiva and lids. The case we describe here is an example of secondary localised amyloidosis occurring in the corneal epithelium.

Previous cases of secondary localised amyloid deposition have been reported. Clinically unrecognisable microdeposits of amyloid have been found in association with such conditions as basal cell carcinoma, Bowen's disease,³ and conjunctival sarcoidosis.⁴ Microdeposits have also been seen in corneas affected with a variety of disorders such as retrolental fibroplasia, phlyctenular keratoconjunctivitis, keratoconus, and penetrating trauma.⁵⁻⁷ Chumbley and Peacock⁸ reported a case of a 25-year-old woman with bilateral trachoma who developed bilateral painless massive conjunctival swellings over two years. This tissue was found to show typical staining characteristics of amyloid and contained a heavy plasmacytic infiltration. The trachoma provided the setting in which the amyloid reaction developed.

Blodi and Apple⁹ described a 66-year-old man with a six-month history of a subconjunctival lump in the palpebral fissure. This was found to be formed of amyloid. However, in this case the patient suffered from rheumatoid arthritis, and though there was no evidence of systemic amyloidosis there was a suggestion that this was an example of secondary systemic amyloidosis rather than of secondary localised amyloidosis. In 1984 Borodic *et al.*¹⁰ described a 30-year-old female who presented with blepharoptosis secondary to localised non-familial amyloidosis. Amyloid was found in the tarsus and tarsal conjunctiva. The abnormal tissue showed the apparent accumulation of proteins similar to fragments of immunoglobulin polypeptides with the amyloid

matrix, though previously such a finding was thought to be restricted to primary systemic amyloidosis.

In summary there seems to be a wide variety of conditions in which amyloid is deposited, but it still remains rare in the ocular tissues. Our case of secondary localised amyloidosis in the cornea is unusual.

Our thanks are due to Dr D Parrish and Dr M Lesna for supplying the histological findings and photographs.

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Purtscher's retinopathy and fat embolism

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SUMMARY A 19-year-old woman who sustained multiple trauma but no head injury developed fulminant fat embolism syndrome (FES). Her neurological deterioration was associated with cerebral oedema and the concomitant Purtscher's type retinopathy. We suggest that the pathogenesis of the retinopathy and of the cerebral oedema are the same and that Purtscher's retinopathy and retinopathy of the FES are indistinguishable.

Retinopathy associated with extraocular trauma was first described by Purtscher.¹ Retinal changes have also been noted to occur in some patients with the fat embolism syndrome.² Here we describe a patient with fat embolism syndrome (FES) in whom retinopathy occurred concomitantly with cerebral oedema.

Case report

A 19-year-old female sustained fractures of her lower limbs and pelvis. She incurred no head injury and was fully alert on admission to hospital. Six hours later her fractures were immobilised under general anaesthesia, from which she recovered completely.

Eight hours postoperatively she began to develop signs of FES, including pyrexia (38°C), tachycardia, skin petechiae, oliguria, hypoxaemia with pulmonary infiltrates on chest X-ray, anaemia, and a coagulopathy. She became rapidly and deeply comatose in association with cerebral oedema, demonstrated by CT scan (Fig. 1). She required tracheal intubation and mechanical ventilation for her cerebral oedema. By the seventeenth day neurological improvement allowed removal of the endotracheal tube. She continued to improve and was discharged from hospital six weeks after the injury with no neurological deficit.

At the time of admission her fundi had been normal, but after 24 hours cotton-wool spots were noted within two disc diameters of the discs. After a

further 48 hours flame shaped haemorrhages appeared adjacent to the cotton-wool spots. The retinopathy remained unchanged for several weeks (Fig. 2) but eventually resolved completely, and both eyes had normal visual acuity on her discharge from hospital.

Discussion

Purtscher's retinopathy is classically described as consisting of cotton-wool spots and haemorrhages developing within one to two days of extraocular trauma and unaccompanied by systemic manifestations.^{1,2} Marr and Marr,² in distinguishing between Purtscher's disease and fat embolism, state that the retinopathy of FES occurs after one to two days and consists of cotton-wool spots, haemorrhages, and retinal oedema accompanied by systemic manifestations. It has been suggested that Purtscher's disease follows head and chest injuries and the retinopathy of FES follows fractures of the long bones.

The proposed distinguishing features between Purtscher's retinopathy and fat embolism syndrome appear therefore to relate to the nature of the precipitating trauma and whether or not the systemic features of FES are present. However, it is now realised that FES is not specific to a particular injury and may be precipitated by a variety of injuries, including minor injuries to the head, chest, or even soft tissue.³ Moreover the clinical syndrome associated with fat embolism is variable: fever, pulmonary infiltrates, neurological changes, and petechiae are the most common features,⁴ but there is no pathog-

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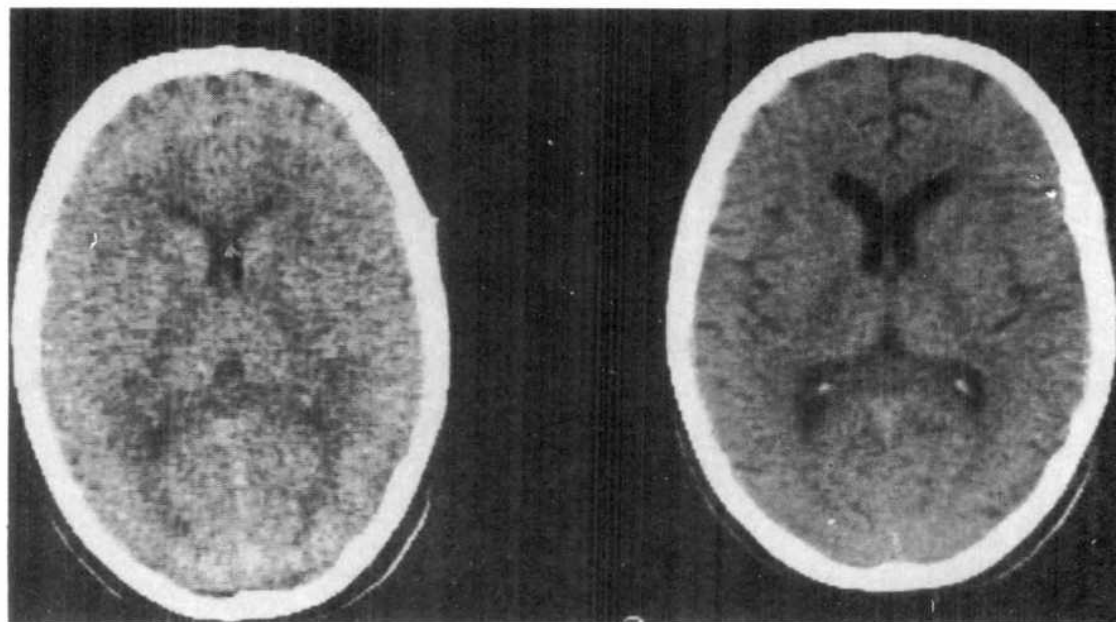


Fig. 1 A CT scan 18 hours after admission to hospital (left) shows an absence of sulci and compression of the lateral ventricles, indicating cerebral oedema. By day 14 the cerebral oedema had resolved (right).

nomonic sign or test. It would appear therefore that the basis for distinguishing between these retinopathies on clinical grounds is tenuous.

The underlying pathology of the FES is incompletely understood, but the evidence suggests that fat

emboli result both from the release of fat from damaged long bones and from coalescence of fat globules in the circulation following the disruption of blood lipid stability.⁵ Loss of stability appears to be secondary to the neurohumoral stress response, as is also a generalised increase in blood concentration of free fatty acids. Endothelial damage results from toxic free fatty acid and from capillary obstruction by fat globules, with associated platelet aggregation, release of vasoactive substances, and production of a coagulopathy.^{5,6} Loss of capillary integrity is the likely cause of the widespread microinfarction and haemorrhage seen in various tissues, including the brain, on post-mortem examination of patients with the fulminant form of FES.⁷

It is now known that the cotton-wool spots of Purtscher's disease are due to microinfarction of the nerve fibre layer of the retina.⁸ It is possible therefore that Purtscher's retinopathy consisting of microinfarction and haemorrhages is another tissue manifestation of FES.

In the case reported here Purtscher's type retinopathy, cerebral oedema, and multiple system manifestations of FES developed simultaneously. It is likely the same pathophysiological sequence unfolded in the systemic and cerebral circulation and the retinal microcirculation, the retina providing the classical window to the cerebral vascular bed.

This case suggests that the retinopathy originally

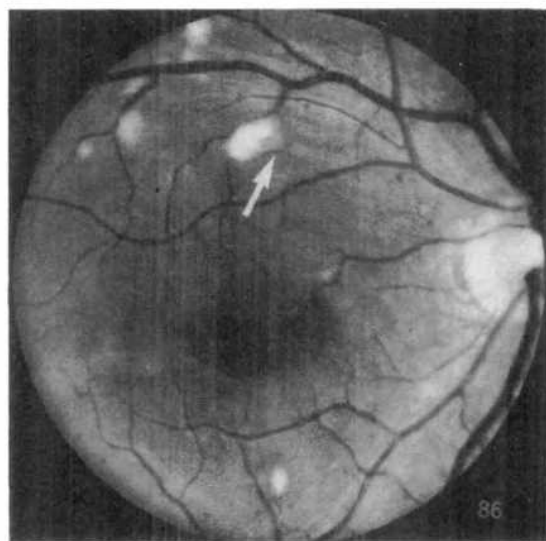


Fig. 2 A fundus photograph taken three weeks after admission to hospital shows areas of cotton-wool spots with adjacent intraretinal haemorrhage (arrow).

described by Purtscher, which we termed traumatic retinal angiopathy, is indistinguishable from the retinopathy of FES. The simultaneous occurrence of cerebral and retinal microangiopathic disease in this patient with FES suggests they are likely to be the result of the FES pathological process. Retinopathy occurring in this setting may be another tissue manifestation of the FES. We would suggest that the traditional differentiation of retinopathy associated with extraocular trauma into Purtscher's disease and FES is arbitrary and without good clinical or pathological foundation.

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Orbital mucormycosis with retinal and ciliary artery occlusions

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SUMMARY A 61-year-old man presented with acute, painful loss of vision in the left eye due to a central retinal artery occlusion. Fluorescein angiography confirmed the central retinal artery occlusion and also identified a nasal posterior ciliary artery occlusion. CT scanning revealed a left medial orbital mass with adjacent ethmoid sinusitis. Transnasal ethmoid biopsy disclosed mucormycosis. A left external ethmoidectomy, maxillectomy, and orbital exploration were performed, after which the patient was treated with daily intravenous amphotericin B for six weeks. Coexistence of retinal and nasal posterior ciliary artery occlusion due to mucormycosis may relate to their common origin from the ophthalmic artery. Treatment without exenteration was successful.

Patients with orbital mucormycosis commonly present with abrupt visual loss, orbital pain, and facial hypoaesthesia. Signs of orbital mucormycosis include chemosis, periorbital cellulitis, ophthalmoplegia, hypoaesthesia, proptosis, and ptosis.^{1–4} Treatment is generally wide debridement, including exenteration if the orbit is involved. An unusual presentation of a patient with rhino-orbital mucormycosis and management without exenteration is presented.

Case report

A 61-year-old man developed a red eye which was treated with topical Neosporin (neomycin, gramicidin, polymyxin B) ointment. One week later the patient experienced sudden, painful total loss of vision (no light perception) in his left eye. A central retinal artery occlusion was diagnosed three days later when he presented to his ophthalmologist. Extraocular movements were limited in abduction and adduction. CT scanning disclosed a diffuse enhancement at the orbital apex and some mucosal thickening in the left ethmoid sinus. A transnasal ethmoid biopsy was performed followed by a pulse of corticosteroid (prednisone, 120 mg daily) without

improvement. The ethmoid biopsy disclosed non-septate hyphae.

The patient was transferred to the orbit service at the University of Washington, Seattle. Visual acuity was 20/20 in the right eye and no light perception in the left eye. The left pupil was dilated and amaurotic. Extraocular movements were limited in abduction and adduction with normal forced ductions. The conjunctiva was slightly injected, but there was no proptosis. Ophthalmoscopy showed the right eye to be normal, while the left fundus had opacification of the superficial layers of the retina with a macular cherry-red spot. The veins showed stasis and the arterioles were collapsed with segmentation (Fig. 1). The retinal circulation was absent on fluorescein angiography. The normally fluorescent temporal choroid was demarcated from the unfilled nasal choroid by a well defined margin running vertically between the disc and macula (Fig. 2).

Serial axial head and orbit CT scans disclosed a left retro-orbital enhancing soft tissue mass along the posterior and medial orbit. The extraocular muscles were poorly defined in the region of the mass. The globe did not appear displaced. The optic nerve was thickened and showed enhancement of the sheath. Abnormal soft tissue density was present within the left maxillary, ethmoid, and inferior frontal sinus (Fig. 3).

The past medical history included chronic active

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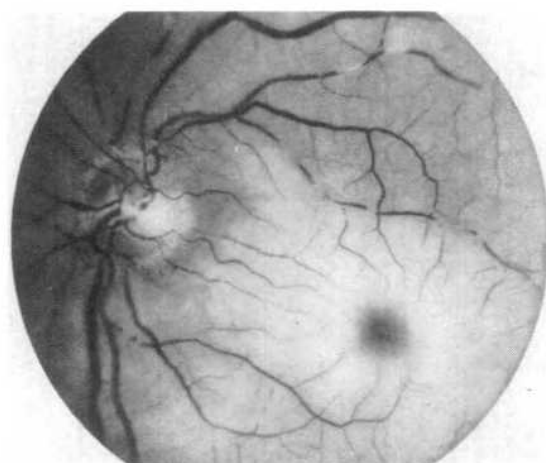


Fig. 1 Left central artery occlusion shows superficial retinal oedema with a macular cherry-red spot, venous stasis, and arteriolar collapse with segmentation.

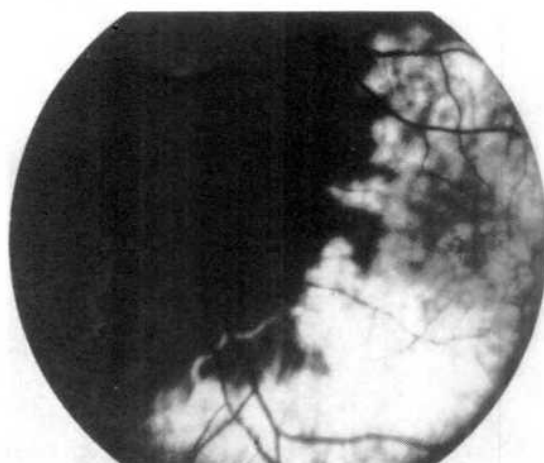


Fig. 2 Fluorescein angiography shows absence of fluorescence in the retinal vessels and nasal choroid. Normal fluorescence is present in the temporal choroid. A well defined vertical margin separates perfused and non-perfused choroid.

hepatitis, confirmed twice by liver biopsies, six and a half years previously. The patient had been treated continuously with corticosteroids for the past year, most recently with 20 mg of prednisone daily. Because a metyropone suppression test disclosed suppressed adrenal function, he was continued on a

maintenance dosage of 5 mg of prednisone daily. Steroid induced diabetes mellitus was being treated by diet. On admission to hospital his fasting blood glucose was 12.6 mmol/l (227 mg/dl). The blood glucose was regulated with insulin while he was in hospital. The cerebrospinal fluid was normal, and cultures from it negative.

The patient underwent a left external ethmoidectomy and Caldwell-Luc maxillectomy. The posterior orbit was explored and found to be normal. Histopathological examination of the tissue from the ethmoid sinus disclosed fragmented non-septate hyphae compatible with mucormycosis (Fig. 4). The orbital biopsy did not show any fungal elements. Cultures of the biopsy material did not grow any organisms.

The patient completed a six-week course of intravenous amphotericin B. He fully recovered except for blindness in the left eye. CT scanning one year later showed the orbital mass unchanged, probably due to fibrosis.

Discussion

Mucormycosis is a known cause of central retinal and ciliary artery occlusion. Ferry and Abedi⁴ described an exenteration specimen of rhino-orbital-cerebral mucormycosis with thrombosed ciliary arteries next to a necrotic optic nerve. Brown *et al.*⁵ reported one of eight cases and Bullock *et al.*⁶ one of two cases with acute obstruction of the retinal and choroidal circulations in orbital mucormycosis which were not confirmed by fluorescein angiography or by histo-

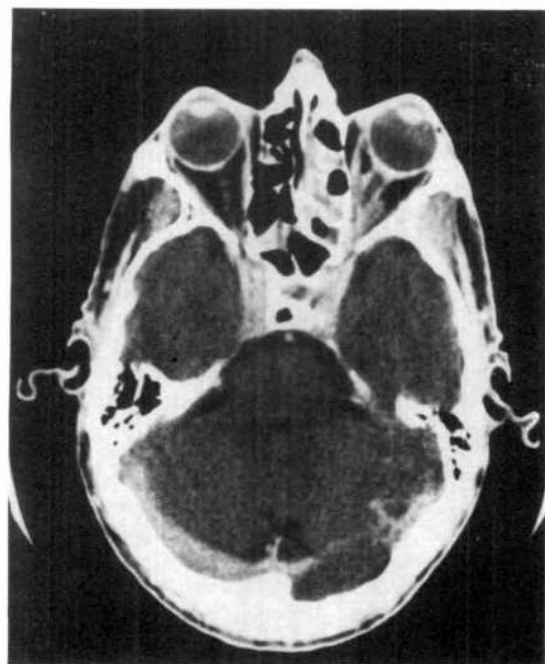
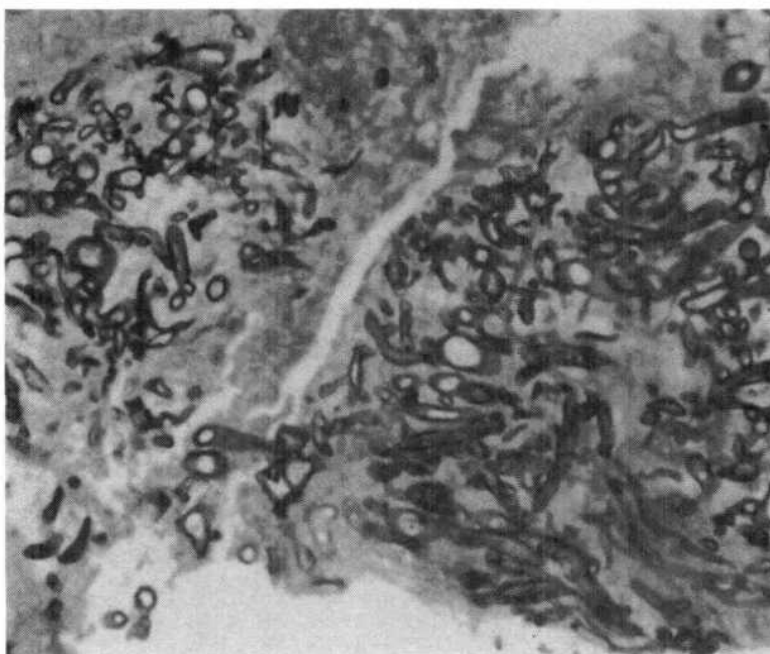


Fig. 3 CT scan shows an enhancing tissue mass along the posterior and medial aspects of the orbit, a thickened optic nerve with tramline enhancement, and soft tissue density within the left ethmoid sinus.

Fig. 4 Biopsy from left ethmoid sinus reveals fragmented non-septate hyphae consistent with mucormycosis. (Gomori silver methenamine, $\times 60$.)



pathology. However, in our case central retinal artery and choroidal artery occlusions due to mucormycosis were confirmed by fluorescein angiography.

Mucormycosis causes a necrotising vasculitis by infiltrating the walls of blood vessels. Secondary thrombosis of the vessel lumen occurs, resulting in infarction.⁷

The central retinal artery branches from the ophthalmic artery near the apex of the orbit. It runs forward and pierces the infranasal dura of the optic nerve 8 to 15 mm behind the globe. Two additional large arteries branch from the ophthalmic artery near the orbit apex, each subdividing into 8 to 10 ciliary branches, which pierce the sclera round the entrance of the optic nerve.⁸ The central retinal artery and the nasal short posterior ciliary artery arise from a common trunk of the ophthalmic artery in 40% of cases. This common trunk divides into the central retinal and nasal ciliary arteries at some distance from the ophthalmic artery. In other, less common, configurations the central retinal artery may arise in common with the temporal posterior ciliary artery or with both posterior ciliary arteries.⁹

The short posterior ciliary arteries are arranged segmentally with each branch supplying a localised area of choroid.¹⁰ A choroidal watershed area is present where the territories of distribution of nasal and temporal posterior ciliary arteries meet between the fovea and nasal border of the optic disc.¹¹ Our patient probably had the most frequent pattern of a

common branch subserving the nasal choroid and central retinal artery. Presumably the central retinal artery and nasal posterior branch were occluded by a mucormycotic necrotising vasculitis, whereas the temporal posterior artery escaped a similar fate.

Most patients with rhino-orbital mucormycosis have a predisposing systemic disease. 80% of patients have diabetes mellitus, generally with excessively raised blood glucose levels often with ketoacidosis.¹ A common factor in many other predisposing states is metabolic acidosis with renal failure or gastroenteritis in infants.² Rhino-orbital mucormycosis has also been found in patients on chemotherapy or immunosuppressive therapy.^{1,3,7} Mucormycosis has been reported occasionally in otherwise healthy individuals.^{2,12} Multiple risk factors were present in this case, including chronic active hepatitis treated with corticosteroids and diabetes.

The sinuses and nose are usually the initial site of infection. Orbital involvement can occur by contiguous spread through normal foramina in the medial wall. The fungi invade blood vessels, causing thrombosis and infarction of the orbital tissues.¹

CT findings in orbital mucormycosis include soft tissue masses in the orbit, thickening of the medial rectus muscle, and proptosis.^{2,13} In our case CT scanning showed a poorly margined soft tissue mass in the apex of the orbit, poor definition of the extraocular muscles in the region of the mass, and a thickened optic nerve with marginal enhancement.

Successful treatment of rhino-orbital mucormycosis includes: (1) early diagnosis; (2) aggressive surgical debridement including exenteration, if necessary; (3) establishment of adequate sinus drainage; (4) intravenous amphotericin B; and (5) control of the predisposing systemic disease.^{1-4 5-7 12-15}

Early diagnosis of rhino-orbital mucormycosis is crucial for a successful outcome, allowing prompt initiation of appropriate treatment. Debridement of local areas of infection and necrotic tissue, with drainage of infected paranasal sinuses, is important because local vascular thrombosis prevents systemically administered drugs from reaching the infected tissues. Exenteration is not, however, required in all cases of orbital mucormycosis. Bullock *et al.*⁶ reported two cases of rhino-orbital mucormycosis treated successfully without exenteration and with sparing of vision. Eight cases of rhino-orbital mucormycosis managed successfully without exenteration were reported by Kohn *et al.*⁷

The survival rate among patients with mucormycosis not treated with amphotericin B was 14%, whereas 57% of the patients treated with amphotericin B survived.¹ In our case retinal artery occlusion was noted five days before initiation of intravenous amphotericin B. Exenteration was not performed because of the normal appearance of the orbital contents and no evidence of fungal elements on biopsy. The patient had been treated with amphotericin B for two days preceding the biopsy, which may explain the absence of fungal elements in the orbit. He recovered but without return of vision. CT scanning one year later showed the orbital apex appearance unchanged; the persistent mass is probably due to fibrosis. The CT appearance, therefore, was not a reliable indicator of the adequacy of therapy.

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Morning glory syndrome associated with marked persistent hyperplastic primary vitreous and lens colobomas

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SUMMARY A case of morning glory syndrome with striking persistence of primary vitreous is presented. The hypothesis that the syndrome is an expression of abnormal closure of the embryonic fissure is substantiated by the coexistence of lens colobomas. Furthermore, the marked primary vitreous hyperplasia shows the way in which persistence of primary vitreous influences the clinical expression with respect to optic pit and colobomas of the optic nerve.

Many associations between morning glory syndrome (MGS) and other ocular and non-ocular abnormalities in the same and in the fellow eye have been reported.¹⁻²² Particular forms have been described, such as acute morning glory,²¹ contractile morning glory^{17,24-30} and bilateral morning glory with normal visual acuity.³¹ Occasionally morning glory syndrome and primitive vitreal persistence are found in association,^{1,32-34} and some authors consider the terms morning glory and persistence of primary vitreous to the optic disk to be interchangeable.³³

We report a clinical case of MG syndrome associated with pronounced persistence of primary vitreous and lens colobomas in the upper and lower nasal sectors. We believe no similar cases have hitherto been reported.

Case report

A 17-year-old girl was referred with reduced vision in the right eye from birth. It had been attributed to congenital cataract. Routine eye examination showed a visual acuity of 20/2400 in the right eye, which was not improved by lenses. The lens showed a posterior polar cataract and there were colobomas at 2 and 4 o'clock (Fig. 1). There was persistence of primary vitreous, with the ciliary body tightly stretched towards the centre of the pupillary field owing to the traction exerted on it by a whitish mass which represented the primary vitreous (Fig. 2). The

pupillary reflexes were normal, and strabismus and nystagmus were absent. The fundus was examined with difficulty, but it showed (Fig. 3) a peripapillary staphyloma, at the centre of which was a greyish-white tissue mass from which straight, narrow retinal vessels originated and ran from the disc to the periphery of the retina. It was not possible to distinguish between veins and arteries.

A slightly raised pigmented ring could be observed round the staphyloma. Owing to the opacity of the

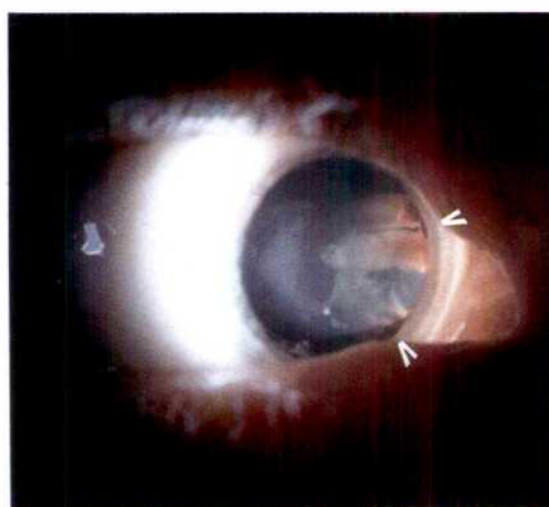


Fig. 1 RE: posterior polar cataract and colobomas of the lens at 2 and 4 o'clock (arrowheads) are particularly evident.

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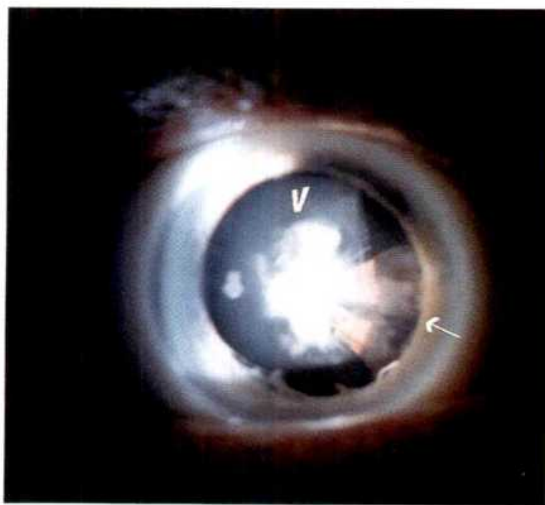


Fig. 2 RE: persistence of primary vitreous (arrowhead) with ciliary body tightly stretched towards the centre of the pupillary field (arrow).

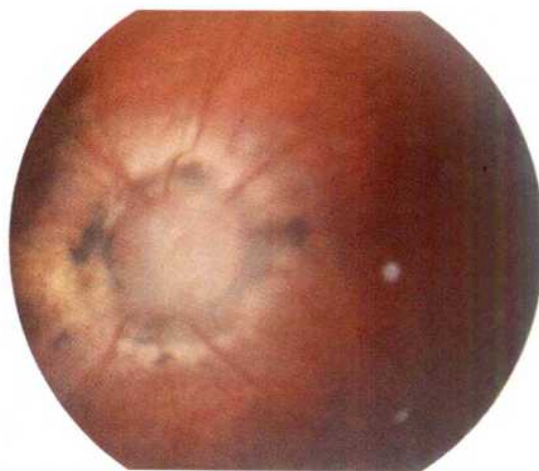


Fig. 3 Typical MGS appearance; a residue of the hyaloid artery is clearly visible on the left.

dioptric media the macula could not be precisely localised. A remnant of the hyaloid artery in the form of a stalk protruded into the vitreous. No abnormalities were detected by gonioscopy.

The left eye was healthy, with VA 20/20.

Standardised echographic examination carried out according to Ossoinig¹⁵ revealed an axial eye length (AEL) within normal limits (anteroposterior=23 mm) and a lens of normal dimensions in the right eye.

B scan echography revealed a morning glory disc filled with acoustically dense material and also hyaloid artery residue.

Discussion

It is debatable whether MGS represents a single entity or whether it is one of many expressions of the same pathogenetic stimulus. We do not agree with the hypothesis that it is a single entity caused by the persistence of the cavity extension of the optic cup in the optic stalk.¹⁷

The present report is thought to corroborate the hypothesis that MGS represents an expression of the abnormal closure of the embryonic fissure (which is suggested by the presence of lens colobomas in the nasal sectors, particularly the inferior sector in the case here described), and we would stress the role of the persistence of primary vitreous in the determination of MGS.

In view of the clinical similarities, and considering the timetable of embryological development of the optic nerve, we believe that MGS represents the clinical form of a pathogenetic process, namely, the

abnormal closure of the embryonic ocular fissure. This has a variety of clinical expressions ranging from MGS to optic pit,^{10,14,36} which can, however, be included in the family of optic nerve colobomas.^{13,34,37,38}

We suggest that the mass of whitish tissue which is ophthalmoscopically visible (and clearly demonstrable with B scan echography) on the abnormal MGS disc corresponds to highly vascularised connective tissue in the area normally occupied by the physiological excavation deriving from the primitive hyaloid system.

Different degrees of the persistent hyperplastic primary vitreous process give rise to a spectrum of clinical expressions. They range from slight (which have been classified erroneously, in our opinion, as distinct clinical and embryological forms, peripapillary staphylomas¹⁷) to conspicuous forms, with a noticeable mass of hyperplastic primary vitreous and with the classical appearance of ciliary body stretched towards the centre of the pupillary field, as described in our case. This range includes intermediate manifestations such as the persistence of lens tunica vascularis (Gass), the extension of vascular branches from the abnormal disc to the posterior lens surface,^{14,34} and the protrusion of fibrovascular tissue into the anterior vitreous, which does not reach the posterior capsule.³⁴

For these reasons, even though the pathogenesis of MGS is still not ascertained—whether there is a mesenchymal abnormality resulting in faulty closure of the posterior scleral wall or abnormal closure of the embryonic fissure, or both³⁹ we support the unitary hypothesis that MGS, optic pit, and optic nerve colobomas are expressions of a single pathogenic process. The persistence and hyperplasia of the

primary vitreous is a fundamental condition of the MG disc and has a great variety of clinical expressions, ranging from the mere presence of whitish tissue on the optic disc surface in the case of simple persistence of the hyaloid artery to more complex clinical pictures.

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Polaroid print film for fluorescein angiography

SIR, For 12 months we have been using high speed Polaroid print film for 'instant' recording of fluorescein angiography and feel this might be of interest to your readers. The main problem with using conventional film to record fluorescein angiography is that there is an inevitable delay while the film is developed. In our experience, even with an automatic film processor, this can lead to delay in assessment and treatment of patients.

The use of direct positive Polaroid film for fluorescein angiography has been described by Jonasson,¹ but this method requires a special kit for development and takes several minutes of processing time. We have found that Polaroid print film, used with a conventional Polaroid print film back, is an inexpensive means of producing 'instant' recording of fluorescein angiography.

The film that we have used is 612 Polaroid print film, which has a film speed of 20000 ASA and is sold commercially for recording oscilloscope traces. It is designed to be sensitive particularly to blue-green and yellow light, making it ideal for recording fluorescein angiography. We have used it with the Zeiss fundus camera in the Polaroid back, and it requires a processing time of 30 seconds, depending on the room temperature, after which the film is normally peeled apart. The print requires to be coated with a protective chemical, which is provided with the film.

The quality of the resulting photographs is acceptable for assessment of patients and is useful in situations where immediate recording of the angiogram is necessary (Fig. 1). We have used it to assess patients requiring urgent laser

treatment to choroidal neovascular membranes and for diabetic maculopathy.

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Eikenella corrodens infection

SIR, The article by Kelly and Eliason¹ prompts us to report another case of keratitis due to *Eikenella corrodens*, a normal commensal of the oropharynx. A 75-year-old man presented with a two-week history of a discharging sore red eye. Vision was reduced to hand movements, and examination revealed a large paracentral semicircular area of ulceration and stromal infiltration. There was a marked degree of flare and cellular reaction in the anterior chamber but no hypopyon. Material was taken from the corneal lesion for examination and treatment started with subconjunctival methicillin 500 mg and gentamicin 40 mg; following this, gentamicin and chloramphenicol drops were given hourly.

Culture of the corneal scrape on blood agar produced a heavy growth of *Eikenella corrodens*. This was sensitive to penicillin, tetracycline, erythromycin, and chloramphenicol. By the time these results were known there was already obvious improvement in the eye. Treatment was continued with gradual resolution and an improvement of vision to 6/36. Although he denied any previous history of eye problems, the patient was a vague and inconsistent historian, who lived alone and had poor hygiene.

Examination of the eye had revealed an area of conjunctival adherence to the medial limbus, suggestive to some previous injury or inflammatory episode.

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Reference

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Book reviews

Ophthalmic Terminology: Speller and Vocabulary Builder. 2nd Ed. By HAROLD A STEIN, BERNARD J SLATT, RAYMOND M STEIN. Pp. 367. £18.50. Blackwell: Oxford. 1987.

This book is aimed at non-medical personnel and at doctors new to the field of ophthalmology. The text is divided into several parts, which deal with basic sciences, refraction,

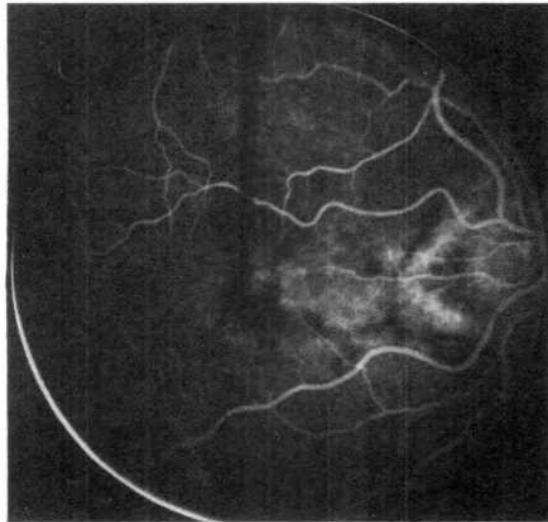


Fig. 1 Fluorescein angiogram of patient with angioid streaks recorded on high speed polaroid print film.

spectacles and contact lenses, disorders of the eye, surgery of the eye, and ophthalmic tests and devices. The chapters on specific topics, such as anatomy, refraction, and glaucoma, are well written, with a lively introduction which is followed by an alphabetical glossary of ophthalmic terms. Having defined each term, the authors then explain the derivation of the more commonly used ophthalmic expressions.

There are many illustrative line drawings, which are simple and clear. However, the black-and-white clinical photographs are often poorly reproduced.

There is no doubt that this is a most useful book for nurses, secretaries, and other non-medical staff, who may use it to check on the correct (American) spelling of ophthalmic terms, and who wish to learn more about the basic concepts of ophthalmology. ZDENEK J GREGOR

condition tends to lead one astray and detract from the main topic of the chapter. The illustrations are in black-and-white and rather few in comparison with the coloured plates now expected to accompany an undergraduate textbook.

There is no mention, beyond light fixation and the E test, of testing vision in children and handicapped patients. At least a reference to the Sheridan-Gardiner test and preferential viewing would have been expected. There are occasional omissions of this type, but on the other hand there is a section on child abuse, and a delightful classification of retinal lesions into red, white, and black.

Postgraduate readers and ophthalmologists at all levels will derive benefit from reading this book. It does, however, require a tenacious undergraduate to assimilate the mass of information presented. It is a useful addition to any medical library. G V CATFORD

Neuro-Ophthalmology Now! Edited by J LAWTON SMITH. Pp. 389. DM 124.00. Springer-Verlag: Berlin. 1986.

This book contains a miscellany of articles with a neuro-ophthalmological theme. The reader will find case reports and original articles (some of which have been previously published in the *Journal of Clinical Neuro-ophthalmology*). There are accounts of radiological and other special techniques and review articles.

Dr Lawton Smith has an idiosyncratic and evangelical editorial style which I found entertaining. He is clearly not averse to criticising his contributors, and although I did not often find myself agreeing with his comments he provides food for thought.

Anyone with an interest in neuro-ophthalmology will find something of interest in this collection. Personally I found the review article on disorders of visual fixation by J A Sharpe and W A Fletcher and a chapter on Wernicke's encephalopathy by J B Selhorst most interesting. It is more a book for an afternoon's browsing than one likely to be referred to frequently. But this is compatible with the nature of the book, for it is designed to be an update and an interesting read. GORDON PLANT

Handbook of Ophthalmology: A Practical Guide. By THOMAS W GARDNER AND DAVID E SHOCH. Pp. 275. £21.35. Prentice/Hall: Hemel Hempstead, Herts. 1987.

This softback book of 275 pages is a compact manual of problem orientated material, divided into 19 chapters. There is a mass of information, so that even the inside covers are utilised with Amsler and near visual acuity charts. Prior to the index is a useful glossary. A simple chapter on basic anatomy introduces the subject. This is followed by chapters on symptoms and clinical examination of the visual system.

Throughout the book the text is basic and understandable, which is admirable for the non-ophthalmologist. Each topic is evaluated, and the differential diagnoses are then reviewed in depth as to cause, investigation, and treatment. This is excellent for the postgraduate but can be confusing for the undergraduate student, as the description of each

News

Biomaterials

The first Interdisciplinary Symposium on Biomaterials in ophthalmology will be held on 1-4 September 1989 at Bologna, Italy. Details from either the Scientific Secretariat, Dr Piera Versura, Institute of Ophthalmology, Via Massarenti 9, 40138 Bologna, Italy; or the organising Secretariat, Studio E R Congressi, Via Riva Reno 47, 40122 Bologna, Italy.

Chinese medicine

The Second World Symposium of Ophthalmology and Traditional Chinese Medicine will be held in March 1990 at Peking (Beijing). Details from ESOTCM Secretary, Service Ophtalmologie, Chic Tarbes - BP 1330, 65013 Tarbes Cedex, France.

Ophthalmology in Singapore Master of Medicine (Ophthalmology)/ FRCS (Edinburgh)

The School of Postgraduate Medical Studies of the National University of Singapore will be conducting a two-week full-time course in advanced ophthalmology for qualified medical practitioners who wish to prepare for the FRCS examination in one of the Royal Colleges. The course contents include modules on glaucoma, paediatric ophthalmology, oculoplastics, vitreoretinal disease, corneal and lens disease, and neurophthalmology. There will also be examination style short cases and examination simulation vivas and question papers. The dates of the course and examination are as follows: Two-week advanced course in ophthalmology, 13-24 November 1989; Conjoint M Med (Ophthalmology)/FRCS (Edinburgh) examination, 11-15 December 1989 (to be held in Singapore). Further information from the Secretary, School of Postgraduate Medical Studies, National University of Singapore, Lower Kent Ridge Road, Singapore 0511.

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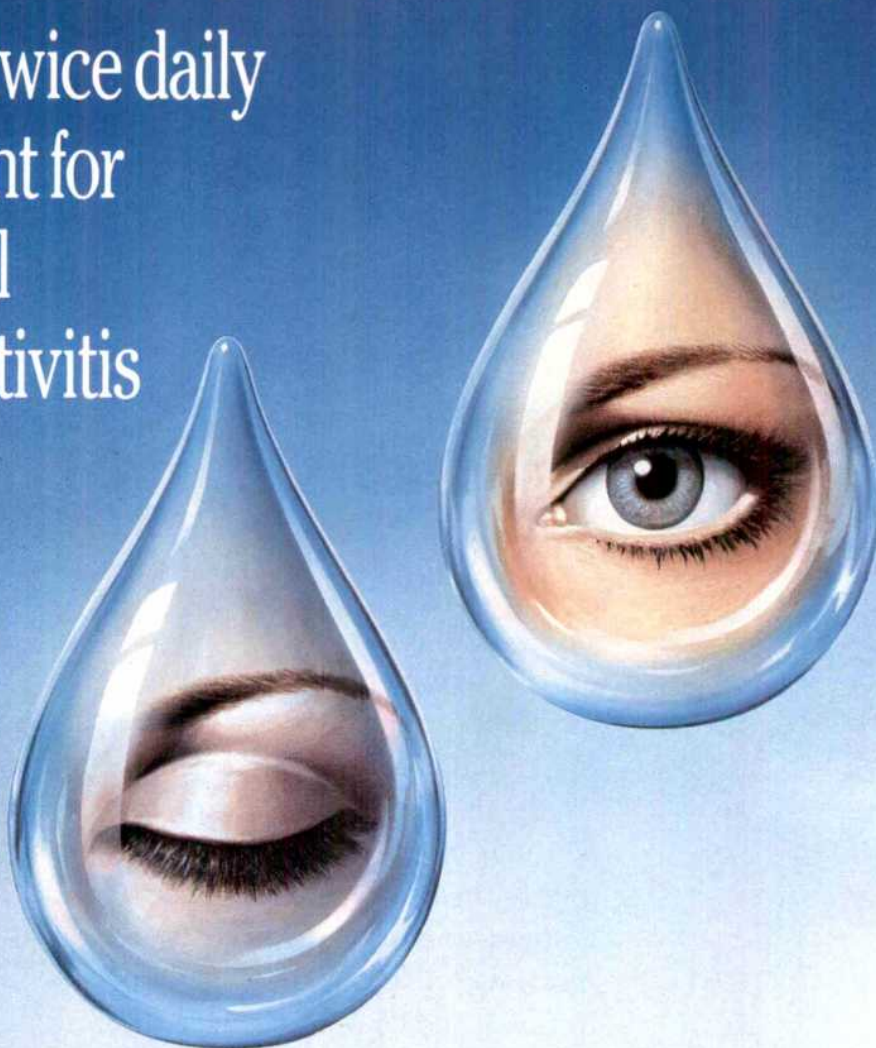


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Editorial: Prognosis in ocular melanoma

The following note was received after we went to press with last month's issue. It is the editorial which should have appeared in that number and it would be a great pity to miss it, since it answers many of the questions asked in the stopgap editorial. It illustrates nicely the difference in interpretation of a difficult subject between the ordinary clinician and the specialist.

* * *

There is no doubt that the survival prospects of individuals who develop uveal melanoma are better when this tumour arises in the iris than when it does so in the ciliary body or the choroid. The relatively benign behaviour of iris melanomas in comparison with the behaviour of those which develop at other sites within the uveal tract may be explained by special features of their clinical presentation and by their cytological characteristics.

The experience from posterior melanomas is that large tumour size is the single most important clinical indicator of a poor prognosis for survival,¹ though a large volume is also closely linked with epithelioid cell type.² Iris melanomas are externally visible, and this probably accounts for their tendency to be diagnosed at a younger age³⁻⁵ and when they are smaller than melanomas elsewhere in the eye.⁶ The better outlook associated with iris melanomas may depend substantially on their tendency to present at an earlier stage in their development.⁷ The most important cytological indicator of a poor prognosis for posterior melanomas is the presence in the tumour of a high proportion of epithelioid cells.^{8,9} Iris melanomas are notable for having few epithelioid cells and a preponderance of naevoid or spindle A cells of doubtful metastatic potential, so that the division between a benign and malignant tumour is less distinct than elsewhere in the uvea.⁵ This feature of iris melanomas led one author to reclassify 87% of a group of iris melanocytic tumours, previously diagnosed malignant on histological criteria, as benign naevi.¹⁰

The accepted treatment of an iris melanoma which is deemed to have malignant potential is surgical excision. Sector iridectomy is recommended for localised tumours not involving the drainage angle and without evidence of dispersion of melanoma cells within the eye. Enucleation is reserved for diffuse iris melanomas and those with intraocular dissemination. Local surgical excision of an iris neoplasm is asso-

ciated with ocular morbidity, and most melanocytic tumours in this location pose no threat to life or to the function of the eye. Nevertheless it has been shown that some 10% of iris melanomas which do contain epithelioid cells will metastasise even though they are small.⁶ It follows that there is a need to distinguish clinically between the harmless tumours which require no treatment and the aggressive tumours which constitute a threat to life. Possible clinical indicators of malignancy are large tumour size and evidence of growth, though benign lesions may expand and invade adjacent intraocular structures.^{6,10} Many iris lesions of worrying appearance have been present for a long time, and surprisingly few can be documented to grow over a five-year period of observation.¹¹ Fluorescein iris angiography may define the limits of tumour involvement but is of uncertain value in predicting malignancy.⁶ In one study it was considered helpful in only 50% of cases.¹²

The trend away from immediate surgical treatment of iris melanomas and towards a policy of serial observations to record growth is probably a reasonable compromise, though it may miss some tumours which have epithelioid cells and which cannot be shown to increase in size. The experience from posterior melanomas is much greater than that from anteriorly situated tumours. It is by no means certain that any treatment influences the metastatic rate of posterior uveal melanomas, because it is likely that many lesions have already disseminated while very small.¹³ This observation may also apply to iris melanomas, but, until it can be shown how big a tumour must be before it is too large for excision or destruction to be beneficial to survival, it seems wise to institute active therapy as soon as there is clinical evidence that any uveal tumour is malignant. For iris melanomas, as for those more posteriorly situated, it remains at issue whether eye conserving procedures offer as good survival prospects as enucleation of the eye.

JOHN HUNGERFORD

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Editorial: Retinal vein occlusion and glaucoma

For a long time there has been a tradition among ophthalmologists that occlusion of the central retinal vein (CRVO) is more common in cases of primary glaucoma, even of a mild degree, than in the rest of the population. However, such cherished ideas do not always bear close examination.

Verhoeff¹ found CRVO in eight of 39 cases of glaucoma and 'endovasculitis at the level of the lamina cribrosa' in all the others. But these were cases of secondary glaucoma, and it was not until Foster Moore's important monograph in 1924² that primary glaucoma became implicated. It has to be remembered as well that many of Verhoeff's cases, even if they had originally been of primary glaucoma, were in any case terminal in that they came to enucleation, and most of us would accept central vein occlusion as a not unexpected finding in an eye with 'absolute glaucoma'.

Foster Moore's paper, which incidentally is extremely difficult to winkle out from most of the major ophthalmological libraries in London, is quite modest in its claims. He studied 31 cases of branch vein occlusion (BVO) and 31 of CRVO. His chief conclusions were that the principal cause of occlusion was arteriosclerosis associated with hypertension and this was more marked in BVO and CRVO. The

second conclusion, which is the one that has received the most attention, was that there was a possible link between primary glaucoma of 'an insidious type' and CRVO. He based this conclusion on the fact that well marked cupping of the optic disc was seen in only one of 31 cases of BVO but 13 of 31 cases of CRVO. There is really not much more evidence than this, but from this fairly shaky start the tradition has originated.

Salzmänn³ in 1933, in another painstaking monograph including a wealth of beautiful clinical and histological drawings, thought that the glaucoma might lead to venous occlusion by causing collapse of the veins. This is quite distinct from the type of glaucoma which results from rubeosis iridis due to retinal ischaemia,⁴ though it was pointed out in 1955⁵ that in some cases primary glaucoma could precede the CRVO-neovascular glaucoma sequence. In the latter paper the author described a number of illustrative cases and followed much the same lines of reasoning as Foster Moore, and pointed out the existence of primary glaucoma in the other eye. In three of the cases pathological specimens became available, but all they showed were changes typical of neovascular glaucoma. It has to be admitted that the paper, which was written by the author of this

editorial, contained no data on the general medical condition of the patients.

The study by Cole, Dodson, and Hendeles in this issue makes it clear that we have to review currently held convictions about the relationship between pre-existing glaucoma and CRVO. These authors have been able to show by a thorough examination of 43 patients with glaucoma and 24 with ocular hypertension presenting with a retinal vein occlusion, and a similar examination of a matched group without glaucoma or ocular hypertension, that the prevalence of the 'other' risk factors for retinal vein occlusions were remarkably similar in the two groups.

It should be emphasised at this point that Cole, Dodson, and Hendeles are not writing solely about unequivocal CRVO but are also including patients with shunt vessels on the disc as assumed CRVO. In addition, cases of branch and hemisphere occlusion (BVO and HVO) are included. They admit in their introduction that the association between CRVO and chronic simple glaucoma is more strongly supported in the literature than BVO, though they state that HVO has been reported as 'unquestionably related'.

I must admit that I have never held the view that BVO was significantly associated, so it comes as no surprise that the risk factors for these cases were the same whether they were in the primary glaucoma group or not. But the fact that the same applied to the CRVO cases certainly came as a surprise. One is perhaps just a little uneasy about the ready acceptance of old bypass vessels as proving prior CRVO, but, even if we were to assume that this was incorrect, nevertheless it does not seem likely that it would have materially altered the conclusions, especially as there

were only six such cases out of the total of 43 'CRVOs'.

After an exhaustive discussion in which consideration is given to every conceivable aspect of the relationship between IOP, blood flow, plasma lipids, blood pressure, treatment for blood pressure, glaucoma and treatment for glaucoma, and optic disc conformation and much more the authors come to the modest conclusion that glaucoma or ocular hypertension may have a less prominent aetiological role in venous occlusion than has been widely believed. I have to say that I believe they are possibly being too modest and their findings may well be confirmed by further studies of this nature to have more of less demolished the primary glaucoma—venous occlusion aetiological relationship which so many of us have accepted for so long, without ensuring that there was adequate evidence. If only I had used a sphygmomanometer as well as a tonometer back in 1955!

REDMOND SMITH

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Editorial: Postoperative eye padding

There was a time when an ophthalmic ward would be full of patients wearing not only one eye pad but two. At Moorfields they were fixed on by means of a brassiere-like contraption, but I have no doubt in other institutions there may have been other methods,

such as swathes of crepe bandage skilfully wrapped round the patient's head or even, in one surgeon's hands for certain patients, a plaster-of-Paris cast.¹ One of my earliest memories as a junior house-surgeon (the title of 'resident' was not in use in those

days) is of a senior surgeon who had just lost vitreous at the end of a classical Graefe knife—no sutures extraction, staring with some annoyance at the section, which was opening and shutting like the mouth of a fish, and then saying 'please put a pad on it.' It is difficult to accept nowadays that an eye could have been abandoned to its fate in such a manner, but one has to realise that sutures, cellulose sponge swabs, and even the idea of cutting vitreous with scissors, let alone with a high-tech machine, were outside the scope of normal ophthalmic surgical practice in those days; I am speaking of almost 40 years ago. But the eye pad had an important, almost mystical symbolic role as signalling the end of the operation and in continuity for the next fortnight or so guarding the patient against the evils of post-operative complications of various sorts. Whether it actually did any good is open to question, but it certainly helped the patient's and the surgeon's morale, and I have to admit that in the case just described the eye did not look too bad the next day. The gradual retreat from the double pad to the single, and in its turn to no pad, has been just a part of the gradual liberation of the patient from the 'doctor's orders' style of medicine in which lack of effective therapy was concealed behind a facade of impressive regulations, ceremonials, and treatments of dubious value.

The article on page 699 of this month's issue reminded me of the vitreous loss incident mentioned above and prompted me in turn to try to remember when I personally changed my attitude to eye padding. The first change would have been from double to single padding and the second to giving up the pad in favour of the cartella shield. I believe I may have given up double padding about 20 years ago but single-padding a considerable time later, probably

only a few years ago. I think that subconsciously I have always been a bit doubtful about padding, but nowhere have I felt this more strongly than in the case of postoperative hypotension with wound leakage or excessive subconjunctival drainage following anterior segment intraocular surgery. Squeezing out even more aqueous humour by the application of a firm pad and bandage has always seemed to me an inappropriate form of treatment or, to put it more bluntly, rather stupid.

However, one must not be too critical of padding. Many years ago I did an operation for strabismus on a charming ophthalmic nursing sister from my own hospital. As one would expect in such an important patient the first operation was not a complete success and a second had to be performed. The point of the story is that on one occasion we padded the eye and on the other we did not. I cannot remember if we padded the first or the second time, I rather think it was the second. Anyway she was quite definite in her opinion, the time she had the pad on postoperatively she was much more comfortable. This was clearly an inadequate scientific experiment, but nevertheless it convinced me that pads certainly have their uses, and one should not forget that, all other things being equal, the patient's comfort has to be remembered. It comes as no surprise, on reading the current article, to learn that the pad probably makes no difference to the bacteriology of the postoperative eye, and it seems that we are left with the final conclusion that to pad or not to pad is probably not a matter we should lose too much sleep over. Maybe we should leave it to the patient to decide.

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Medical conditions underlying retinal vein occlusion in patients with glaucoma or ocular hypertension

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SUMMARY Forty-three patients with glaucoma and 24 patients with ocular hypertension presenting with a retinal vein occlusion were medically assessed. The prevalence of systemic hypertension was 60.5% in those with glaucoma and 66.6% with ocular hypertension. The prevalence of hyperlipidaemia was 38.1% in those with glaucoma and 37.5% in those with ocular hypertension. These findings were compared with those from a carefully age-sex matched group of patients presenting with a retinal vein occlusion without evidence of glaucoma or ocular hypertension. There were no statistical differences between any of the groups (52.2% had systemic hypertension and 28.8% had hyperlipidaemia). There was also a strikingly high prevalence of systemic hypertension (89%) and hyperlipidaemia (55.5%) in nine of the patients who had evidence of a recurrent retinal vein occlusion associated with glaucoma, and these prevalence rates were strikingly similar to the rates in patients with recurrence but without glaucoma. The data suggest that glaucoma or ocular hypertension has a less prominent aetiological role in the development of a retinal vein occlusion than underlying medical causes and that full medical assessment is worthwhile.

An association between central retinal vein occlusion and chronic simple glaucoma has been recognised for many years.¹⁻⁶ Similarly, central retinal vein occlusions occur in 3% of patients with ocular hypertension.⁷ The association between branch retinal vein occlusion and glaucoma is less clear.^{1-4,6} However, hemisphere vein occlusion with the obstruction occurring at the edge of the optic cup is considered to be unquestionably related.⁸ From another point of view retinal vein occlusion has well established associated medical conditions, and a comparison between the prevalence in patients with retinal vein occlusion preceded by glaucoma or ocular hypertension, and patients with retinal vein occlusion without evidence of glaucoma or ocular hypertension, may give a hint to the importance of glaucoma or ocular hypertension in the aetiology of retinal vein occlusion.

We therefore performed a study to ascertain the prevalence of associated medical conditions in a group of patients with the combination of retinal vein occlusion and preceding glaucoma or ocular hyper-

tension and compared them with a group of patients presenting with retinal vein occlusion without evidence of glaucoma or ocular hypertension who had been matched for age, sex, and vein occlusion type. The aetiological role of glaucoma or ocular hypertension in retinal vein occlusion and the value of medically investigating these patients is thus considered.

Patients and methods

Sixty-seven patients with retinal vein occlusion together with either glaucoma or ocular hypertension were assessed and divided into two groups. The first group included 43 patients with glaucoma who subsequently presented with a retinal vein occlusion. The second group included 24 patients with ocular hypertension who likewise presented with a retinal vein occlusion. The clinical details are presented in Table 1. Patients were excluded if rubeosis was present at the time of the diagnosis of glaucoma or ocular hypertension.

We defined ocular hypertension as an intraocular pressure (IOP) of greater than 21 mm Hg⁹ in either

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Table 1 Clinical details of the patients with retinal vein occlusion both with and without ocular hypertension or glaucoma

	Glaucoma patients	Isolated RVO comparison	OHT patients	Isolated RVO comparison
Number	43	43	24	24
Sex	25M:18F (1:39:1)	25M:18F (1:39:1)	11M:13F (0:85:1)	11M:13F (0:85:1)
Mean age	68.47 (SD 9.6)	68.79 (SD 9.3)	68.75 (SD 8.5)	69.42 (SD 8.2)
Mean weight	74.41 Kg (SD 11.8)	72.54 Kg (SD 14.0)	71.92 Kg (SD 15.1)	67.28 Kg (SD 14.4)
RVO type	32 CRVO 11 BVO	32 CRVO 11 BVO	15 CRVO 9 BVO	15 CRVO 9 BVO

RVO=retinal vein occlusion. OHT=ocular hypertension. No statistical differences between the groups were found.

eye, noting that, once a vein occlusion had occurred, the IOP in that eye may fall for up to two years.¹⁰ Where possible more than one recording was used to confirm raised IOP; however, most patients had been diagnosed before attending the clinic.

Glaucoma was defined as occurring in an eye with abnormally raised IOP in which there was pathological cupping of the optic disc with corresponding visual field defects. The optic disc may be swollen in retinal vein occlusion and thus may mask the presence and extent of cupping. Likewise there may be visual field defects which could equally be caused by glaucoma or retinal vein occlusion. Allowance therefore had to be made for these diagnostic problems. There were 37 patients with open angle glaucoma, two with chronic angle closure glaucoma, and one with glaucoma secondary to a blunt injury. We also included one patient who had acute angle closure glaucoma and central retinal vein occlusion concurrently despite the fact that the resulting visual field and optic disc appearance was normal, and two patients with low tension glaucoma.

Retinal vein occlusion was diagnosed on clinical grounds. In view of the significant number of patients with glaucoma who develop retinal vein occlusion silently¹¹ we assumed newly discovered shunt vessels on the disc in the absence of orbital disease to indicate the presence of a central retinal vein occlusion. The diagnosis was confirmed by slit-lamp examination, gonioscopy, direct and indirect ophthalmoscopy, and visual field assessment. Retinal vein occlusion was subdivided into a central form, including six patients with shunt vessels on the optic disc, and that of a branch occlusion, which included five patients with hemisphere vein occlusion.

The patients were then examined by a physician, and the following laboratory investigations were

Table 2 Prevalence of medical conditions underlying retinal vein occlusion with and without glaucoma or ocular hypertension

	Hypertension	Hyperlipidaemia	Diabetes
Glaucoma patients	26 (60.5%) n=43	16 (38.1%) n=42	2 (4.9%) n=41
OHT patients	16 (66.6%) n=24	9 (37.5%) n=24	5 (20.8%) n=24
Isolated RVO comparison	35 (52.2%) n=67	19 (28.8%) n=66	5 (7.5%) n=67

OHT=ocular hypertension. RVO=retinal vein occlusion.

For ease of presentation in Tables 2, 3, and 7 the values were used for all the patients with RVO together as a comparison group. No statistical differences were observed between the groups.

carried out for each patient: full haematological profile, blood urea, electrolytes, liver function tests, protein electrophoresis and immunoglobulin levels, fasting lipid profile, blood glucose, chest x-ray, and electrocardiogram (ECG).

The blood pressure was recorded after five minutes' rest in the sitting and supine positions on an Accuson sphygmomanometer and the mean recorded. The diastolic pressure was recorded at the fifth Korotkoff phase.

Hypertension was defined according to the World Health Organisation criteria as a systolic pressure of greater than 160 mm Hg and a diastolic pressure of greater than 95 mm Hg on three occasions, or when a patient was already established on antihypertensive drug therapy. Hyperlipidaemia was defined as a fasting serum cholesterol level of greater than 7.1 mmol/l or a fasting serum triglyceride level of greater than 2.1 mmol/l. Serum cholesterol and triglyceride were measured by standard semi-automated techniques.

The comparison groups were taken from patients attending the same hospital with a retinal vein occlusion alone without evidence of glaucoma or ocular hypertension. They were closely matched for age, sex, and type of vein occlusion, and their clinical details are presented in Table 1. Statistical comparisons were made by the unpaired *t* test, and the χ^2 test.

Results

Tables 2 and 3 show the prevalence and mean values of associated medical diseases in the groups.

No statistical differences were observed in the prevalence of hypertension and hyperlipidaemia between the glaucoma or ocular hypertension groups and the matched groups, and the prevalence rates were also comparable in the glaucoma and the ocular hypertension groups. Diabetes mellitus was relatively uncommon in all three groups.

Table 3 Mean values of systemic and diastolic blood pressure, cholesterol, and triglyceride levels in the major groups

	Mean systolic BP (mm Hg)	Mean diastolic BP (mm Hg)	Mean serum cholesterol (mmol/l)	Mean serum triglyceride (mmol/l)
RVO+glaucoma n=43	166.74 (SD 28.1)	90.26 (SD 10.9)	6.47 (SD 1.3)	1.61 (SD 0.8)
RVO+OHT n=24	166.88 (SD 22.1)	9.17 (SD 7.0)	6.51 (SD 1.4)	1.60 (SD 0.8)
RVO control n=67	169.33 (SD 29.3)	90.76 (SD 13.6)	5.83 (SD 1.6)	1.38 (SD 0.6)

RVO=retinal vein occlusion. OHT=ocular hypertension.

Combining the glaucoma and ocular hypertension groups, we found a high prevalence of abnormally raised fibrinogen (mean 4.33 (SD 1.0) g/l, $n=61$; 37.7% >4.3 g/l), and immunoglobulin levels, especially IgA (mean 2.96 (SD 1.2) g/l, $n=44$; 25% >4.0 g/l). Only 24 patients had their plasma viscosity estimated, but 20 of these had levels of 1.8 cp or more. There were nine patients with raised haemoglobin levels (>16 g/dl), but none had a packed cell volume of greater than 50%. The mean erythrocyte sedimentation rates (ESR) were not significantly raised. Other important medical conditions were also identified in the two groups, and are presented in Table 4.

Nine patients (13.4%) were recorded to be active smokers and 11 (16.4%) past smokers. Four had a moderate alcohol intake; one had a past history of high alcohol consumption.

Nine patients (13.4%) had evidence of a previous retinal vein occlusion in the other eye (that is, recurrent retinal vein occlusion). The prevalence of hypertension and hyperlipidaemia in this group was strikingly high (Table 5). Data are also included showing the prevalence rates in a previous study from the same hospital by Dodson *et al.*¹² of 17 patients with recurrent retinal vein occlusion without evidence of glaucoma or ocular hypertension, and a striking similarity is apparent.

There were 11 patients (16.4%) in the glaucoma

Table 5 Patients with recurrent RVO

	Recurrent RVO with glaucoma or OHT (Present study)	Recurrent RVO without glaucoma or OHT (Dodson <i>et al.</i> ¹²)
Number	9	17
Sex	7M:2F	9M:8F
Mean age	60.66	65.94
Hypertension	8 (89%)	15 (88%)
Hyperlipidaemia	5 (55.5%)	8 (47%)
Hypercholesterolaemia	4 (44.4%)	6 (35%)
Hypertriglyceridaemia	3 (33.3%)	4 (24%)

RVO=retinal vein occlusion. OHT=ocular hypertension.

and ocular hypertension groups combined who had no associated medical conditions. Their mean IOP at the time of diagnosis was compared with that of the remaining patients, apart from those with neovascular glaucoma (Table 5). There was no statistical difference between the mean levels in the two groups. They were higher than 21 mm Hg in the affected eye in both groups (Table 6). A similar result was also seen in the unaffected eye apart from eyes with rubeosis.

The prevalence of associated medical conditions in patients with a central retinal vein occlusion were also analysed separately and compared with the prevalence rates in patients with the branch form. The results are presented in Table 7, and shows a trend towards a slightly higher prevalence of both hypertension and hyperlipidaemia in patients with the branch form, especially hypertension in the ocular hypertensive group.

Shunt vessels on the optic disc may not be conclusive evidence of central retinal vein occlusion. However, removing from the analysis the six patients whose central retinal vein occlusion was diagnosed on the presence of collaterals on the optic disc makes no difference to the results.

Discussion

The relationship between glaucoma and central retinal vein occlusion was first recognised in 1913 by

Table 4 Other associated medical conditions in patients with ocular hypertension or glaucoma

Medical condition	Number
Aortic/mitral valve disease	4
Chronic renal failure	3
Carcinoma (1 on tamoxifen)	3
Chronic lymphatic leukaemia	1
Myeloma	1
Giant cell arteritis	1

Table 6 Comparison between the mean intraocular pressures recorded in a group of patients who had no associated medical conditions and in the remaining patients apart from those with rubeosis

	No associated medical condition	Remainder
Mean IOP affected eye (mm Hg)	24.36 $n=11$	24.24 $n=54$
Mean IOP other eye (mm Hg)	24.45 $n=10$	23.33 $n=49$

Table 7 Prevalence of hypertension and hyperlipidaemia in patients with glaucoma or ocular hypertension with CRVO compared with patients with branch RVO and an isolated RVO comparison group

	Hypertension			
	Glaucoma	OHT	Total	Isolated RVO comparison
CRVO	20 (62.5%) n=32	8 (53.3%) n=15	28 (59.6%) n=47	29 (61.7%) n=47
BVO	6 (54.5%) n=11	8 (88.8%) n=9	14 (70%) n=20	8 (40%) n=20
	Hyperlipidaemia			
	Glaucoma	OHT	Total	Control
CRVO	11 (35.5%) n=31	5 (33.3%) n=15	16 (34.8%) n=46	12 (28.8%) n=46
BVO	5 (45.5%) n=11	4 (44.4%) n=9	9 (45%) n=20	7 (35%) n=20

RVO=retinal vein occlusion. CRVO and BVO=central retinal vein occlusion and branch vein occlusion respectively. OHT=ocular hypertension.

Verhoeff.¹³ Subsequently several authors have reported on the high incidence of retinal vein occlusion in patients with glaucoma. Primary open angle glaucoma is a feature which precedes central retinal vein occlusion, with a prevalence ranging from 5.7% to 65.5%. Most studies show a prevalence between 10 and 40%.¹⁻⁴ In contrast, the prevalence of primary open angle glaucoma in branch vein occlusion appears to be less frequent at between 6.6% and 15%.^{1-4, 6}

Prospective studies have also suggested a link. For example, Dobree found that 4.5% of patients with chronic open angle and closed angle glaucoma, after one to eight years' follow-up, developed a retinal vein occlusion.¹⁴ David *et al.* found a similar rate of 3% in patients with ocular hypertension after one to 11 years.⁷

The explanation for the association between glaucoma and retinal vein occlusion has yet to be elucidated. Some authors have considered that these conditions are not related aetiologically but rather are both manifestations of some underlying vascular abnormality.^{4, 15} Systemic hypertension is not related to chronic simple glaucoma; in fact the mean systolic blood pressure in patients with glaucoma has been shown to be low.¹⁶ There are conflicting reports of the incidence of hyperlipidaemia in patients with glaucoma or ocular hypertension,^{17, 18} though risk factors in low tension glaucoma include hypertension, diabetes mellitus, hyperlipidaemia, and raised blood and plasma viscosities.¹⁹ A similar IOP response to postural changes in eyes with chronic

glaucoma and eyes following vein occlusion was suggested by Williams and Peart to be indicative of an underlying vascular abnormality.²⁰ This may be particularly relevant in the case of retinal vein occlusion not related to raised IOP, as it is well documented that the primary event is endothelial cell proliferation in the vein wall associated either with degeneration of the endothelium and secondary thrombus formation or with severe phlebosclerosis.²¹ The exact mechanism underlying the primary event is not clear, but clinical studies indicate that it is multifactorial, with cardiovascular risk factors such as hypertension and hyperlipidaemia prominent.^{12, 22-24} Other abnormalities have been identified and include abnormal in-vivo platelet function,^{25, 26} hyperviscosity,²⁷ and perhaps increased inflammatory activity.²⁷⁻²⁹

The results in this study do, however, demonstrate that the prevalence of associated medical conditions in patients with retinal vein occlusion either with or without glaucoma or ocular hypertension are markedly similar. This observation holds for hypertension, hyperlipidaemia, diabetes mellitus, and smoking habits. The other abnormalities found with raised fibrinogen, IgA, and plasma viscosity levels are also consistent. The striking resemblance between those patients with recurrent retinal vein occlusion with preceding glaucoma or ocular hypertension and a previously reported group from the same hospital with recurrent retinal vein occlusion alone would also strongly support the similarity between the two groups.¹² These findings imply that glaucoma or ocular hypertension may not be the most important aetiological factor and that the associated medical conditions may be of greater significance.

The relationship between IOP, retinal blood flow, and systemic arterial pressure is complex. Under normal circumstances the ocular blood flow is chiefly determined by the level of the systemic arterial and intraocular pressures, the blood viscosity, and the state of the blood vessels supplying the eyes.³⁰ In response to raised IOP autoregulation occurs, with an increase of pressure in the arteries outside the eye and decreased vascular resistance in the retina to maintain normal blood flow.³¹

It may be that for these patients with a compromised circulation, and possibly compromised autoregulatory mechanisms, a minor rise in IOP is high enough to reduce ocular blood flow sufficiently to propagate stagnant blood flow. This hypothesis is supported by the finding of a reduction in IOP thresholds, normally estimated to be 27-30 mm Hg in patients with chronic simple glaucoma, up to which autoregulation, by increasing arterial pressure with decreased vascular resistance, maintains normal blood flow.³²

Although we do not know the exact IOP at the time of a retinal vein occlusion, available evidence would suggest that the pressure may be raised³³ and that the venous occlusive episode itself subsequently has a lowering effect.¹⁰ Only two patients suffered from low tension glaucoma. However, this may simply reflect the incidence of diagnosed low tension glaucoma in comparison with chronic simple glaucoma. Therefore a minor elevation of pressure with a reduction in retinal blood flow might also contribute to a venous occlusion.

Mechanical compression at the site of the venous occlusion is thought by some to compromise the circulation further.³⁴ In patients with central retinal vein occlusion backward bowing of the lamina cribrosa³⁵ or loss of glial support in a pathologically cupped optic nerve head,³⁴ is thought to be responsible. It has been found, however, that retinal vascular events tend to occur early in the course of the associated glaucoma and not, as might be expected, to be related to the degree of cupping.^{2,35} This again emphasises the more important aetiological role of other factors. Furthermore, no differences between the mean IOPs of patients who had no associated medical condition were found in comparison with the remainder, which implies that even in this group the raised IOPs might still have only a minor role.

Management of a patient with a retinal vein occlusion with or without glaucoma or ocular hypertension should include the identification and treatment of common conditions which appear to have an aetiological role in retinal vein occlusion. Other serious medical disorders, including carcinoma of breast, myeloma, and chronic lymphatic leukaemia, were identified in our group, and emphasise the importance of medical investigation.

Retinal vein occlusion appears to be linked with an increase in vascular causes of death (cardiac and cerebral),³⁶ and there is evidence that treatment of hypertension and hyperlipidaemia can reduce the severity of some of its complications. Identification of these factors should therefore offer an opportunity for effective therapy.³⁷⁻³⁹ Indeed the result in reducing the rate of devastating recurrence of retinal vein occlusion from 10-15%, as previously reported, to 1%, as suggested in a preliminary study after a five-years follow-up,²² is encouraging.

However tenuous the evidence may be, control of the IOP on theoretical grounds should still be considered important. It may also be important to establish the effect of drugs on the capacity of the autoregulatory mechanisms in the retina. Grunwald found that timolol enhances autoregulation of retinal blood flow, and suggested that this may help perfusion following retinal vein occlusions.⁴⁰ Other antiglaucoma drugs may affect this capacity. The

treatment given for controlling systemic hypertension may also affect the control of the IOP, and perhaps autoregulation. These factors need further investigation.

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Is padding necessary after cataract extraction?

D E LAWS, M T WATTS, G R KIRKBY, AND J LAWSON

From the Birmingham and Midland Eye Hospital.

SUMMARY The results of a prospective study to assess the value of padding eyes following cataract surgery are reported. A group of eyes dressed with a petroleum jelly mesh, gauze pad, and cartella shield were compared with a group dressed only with a cartella shield. Study of the eyes and lids before and after operation, including the taking of lid margin and fornix swabs for culture, suggested that there was no significant difference in the bacterial presence between the two groups. The eyes dressed with a cartella shield alone appeared less prone to discharge. The relative merits of different types of dressing are discussed.

The application of an eye pad following cataract surgery is a long established routine. A survey of ophthalmologists in the United Kingdom showed that 92% apply a gauze dressing either alone or in combination with other protection, such as a cartella shield or crêpe bandage.¹ This practice is recommended in a number of standard texts.^{2,3}

The rationale for a dressing in contact with the lids is ill defined, and the practice follows tradition rather than proved merit. This paper presents the results of a prospective study to assess the worth of padding of an eye following cataract surgery. A group of patients who underwent dressing of the eye by conventional pad and cartella was compared with a similar group to whom only a cartella was applied. The state of the eyelids postoperatively was studied, and pre- and postoperative cultures of the lid margin and conjunctival sac were taken to see whether the groups differed in their postoperative bacteriology.

Material and methods

Forty-two consecutive patients scheduled to undergo extracapsular cataract extraction with implantation of an intraocular lens were entered into the study. A standard surgical technique was used with a fornix based conjunctival flap and an ab externo incision. The lid margins and inferior fornix were examined before operation and swabs of these sites taken with a cotton bud soaked in sterile saline. In one patient surgery was deferred owing to frank clinical infection. No others were excluded. Preoperative topical anti-

biotics were then administered in the form of gentamicin eye drops 2-hourly to both eyes during the waking hours preceding surgery. Immediately before operation the lids and periorbital skin were cleansed with aqueous chlorhexidine. Subconjunctival gentamicin (20 mg) and betamethasone (2 mg) were given at the end of the operation. A randomised envelope was then opened to instruct either dressing with a sterile petroleum jelly mesh eye pad, and plastic cartella shield or a sterile cartella shield alone. The eye was dressed accordingly.

On the first postoperative day the dressing was removed and the eye examined at the slit-lamp. The lids were examined for the presence of any discharge, and cultures of the lid margin and inferior fornix were repeated (by the same clinician as did all the preoperative cultures), and swabs were immediately plated on to blood agar. Plates were incubated for 48 hours.

Results

Of 42 patients in the study group one had operation deferred owing to clinically apparent purulent conjunctivitis; cultures subsequently grew α -haemolytic streptococci. Of the 41 others 22 were dressed with a petroleum jelly mesh, gauze pad, and plastic cartella, and 19 with a cartella alone.

Microbiology. Preoperative cultures grew colonies of *Staphylococcus epidermidis*, *Corynebacterium xerosis*, micrococci, diphtheroids, neisseria, other Gram-negative organisms, α -haemolytic streptococci and *Staphylococcus aureus*, as shown in Table 1. Postoperatively no pathogenic bacteria were

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Table 1 Incidence of preoperative positive cultures

Organism	Padded group		Unpadded group	
	Lid No. (%)	Conjunctival sac No. (%)	Lid No. (%)	Conjunctival sac No. (%)
<i>Staphylococcus aureus</i>	3 (14)	2 (9)	2 (10)	0 (0)
α -Haemolytic streptococci	1 (4.5)	1 (4.5)	1 (5)	0 (0)
Diphtheroids	2 (9)	2 (9)	1 (5)	0 (0)
<i>Neisseria</i> spp.	2 (9)	0 (0)	3 (16)	2 (10)
Other Gram -ve	1 (4.5)	1 (4.5)	0 (0)	0 (0)
Micrococci	10 (45)	5 (22.5)	10 (53)	7 (37)
<i>Corynebacterium xerosis</i>	19 (86)	14 (64)	14 (74)	11 (58)
<i>Staphylococcus epidermidis</i>	19 (86)	13 (59)	17 (89)	12 (63)

grown from either the lids or fornices of either the padded or unpadded group, with the exception of a single patient who was dressed with a pad and cartella from whose lids *Staphylococcus aureus* was grown postoperatively.

Similarly, a large number of 'commensals' were absent from postoperative cultures. Those remaining are listed in Table 2. The most frequently present organism was *Staphylococcus epidermidis*, but there was no significant difference in its presence between the two groups.

Condition of the lids. The condition of the eyelids at the first dressing was examined and the presence of discharge noted. There was some discharge in eight out of 22 padded eyes but in only two out of the 19 unpadded eyes. We concluded that those eyes dressed with a cartella alone were less prone to accumulate discharge.

Mechanical complications. One patient in the padded group was found to have a slight wound leak on the first postoperative day. This settled spontaneously after 24 hours. A small peroperative corneal abrasion in one patient in the unpadded group had fully healed by the time of the first dressing. There were no other postoperative complications possibly attributable to the dressing technique.

Discussion

Most ophthalmologists apply an eye pad following cataract surgery as an established routine, presumably in the belief that it affords some degree of protection to the eye from both bacterial and mechanical insult. The aim of this paper was to see if this is the case by comparing two groups of patients undergoing cataract surgery with and without postoperative padding. Lid and conjunctival cultures have shown that there was little difference between the prevalence of 'commensals' postoperatively in the two groups. All the pathogens were eliminated by the prophylactic antibiotics except for one colony of *Staphylococcus aureus* in one patient in the padded group.

We believe it is naive to assume that a gauze pad prevents access of organisms to the eye. Indeed, the warm, moist atmosphere beneath a gauze pad might be thought to provide an ideal culture medium. A Cartella shield alone is likely to prevent the patient contaminating his eye with his fingers.

Mechanical injury to the eye postoperatively is a relatively uncommon complication. We consider that a plastic Cartella shield alone provides as good protection as does a gauze pad and Cartella. The only wound leak occurred in a patient wearing both a pad

Table 2 Incidence of postoperative positive cultures

Organism	Padded group		Unpadded group	
	Lid No. (%)	Conjunctival sac No. (%)	Lid No. (%)	Conjunctival sac No. (%)
<i>Staphylococcus aureus</i>	1 (4.5)	0 (0)	0 (0)	0 (0)
α -Haemolytic streptococci	0 (0)	0 (0)	0 (0)	0 (0)
Diphtheroids	0 (0)	0 (0)	0 (0)	0 (0)
<i>Neisseria</i> spp.	0 (0)	0 (0)	0 (0)	0 (0)
Other Gram -ve	0 (0)	0 (0)	0 (0)	0 (0)
Micrococci	2 (9)	1 (4.5)	4 (20)	1 (5)
<i>Corynebacterium xerosis</i>	0 (0)	1 (4.5)	2 (10)	0 (0)
<i>Staphylococcus epidermidis</i>	10 (45)	9 (40)	8 (42)	6 (32)

and Cartella, though its origin was not thought to be traumatic.

The assessment of comfort is notoriously difficult and inaccurate. In an attempt to provide some objective assessment, however, the presence or absence of a discharge on the lids was assessed: it was less in the absence of a dressing in direct contact with the lids.

A further advantage of a simple Cartella dressing is that two patients spontaneously remarked on their ability to see through holes in the shield. This would be of benefit particularly in patients without useful vision in the fellow eye,⁴ in agitated patients, and in those undergoing day-case cataract surgery.⁵ A transparent Cartella would be ideal (and is now commercially available).

Hartley, describing his own postoperative recovery from cataract surgery, remarked, 'No really efficient protection for the eye after operation appears to have been devised to supersede the Cartella shield.'⁶ Our

findings would tend to support this, and encourage dressing of eyes with a Cartella shield alone.

The authors thank Dr J Harry and Mr J Lawson, of the Department of Pathology, Birmingham and Midland Eye Hospital, for their assistance in this study.

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Warfarin and cataract extraction

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SUMMARY Ten cataract extractions were performed on eight patients for whom warfarin was not discontinued prior to surgery. Three were complicated by hyphaema. No retrobulbar haemorrhages occurred in the four cases given a local anaesthetic. Cataract surgery can be performed successfully without discontinuing warfarin.

It is usual to discontinue warfarin before elective surgery, but for some patients this is not advisable because it would place them at risk of possibly fatal embolism or thrombosis. We reviewed 10 cataract extractions performed on eight patients for whom anticoagulation was not discontinued in the peri-operative period.

Patients and methods

The 10 cataract extractions were performed between January 1985 and May 1988. There were five men and three women aged 66 to 83. The reasons for anticoagulation are shown in Table 1. Three patients were diabetic.

Six operations were performed under general anaesthesia and four under local anaesthesia. Eight were extracapsular cataract extractions, six with posterior chamber intraocular lenses and two in high myopes. Two were endocapsular cataract extractions with posterior chamber intraocular lenses. The British comparative ratio/international normalised ratio (BCR/INR) was measured prior to surgery.

Results

The range of BCR/INR was 1.5 to 4.5 for all 10 operations and the range for the four under local anaesthetic was 1.5 to 3.1 (Table 2). None of the four cases under local anaesthetic suffered a retrobulbar haemorrhage.

A posterior chamber intraocular lens was inserted in all eight cases requiring it.

Three hyphaemas occurred. The first was a small operative hyphaema and cleared by the third post-

operative day. The INR on the day of surgery was 1.5. The second was a small operative hyphaema which cleared by the first clinic appointment at two weeks. The INR was 4.5 on the day of surgery. In the third case a 3 mm hyphaema was present two weeks postoperatively. The INR at the time of surgery was 3.1, and no hyphaema was present immediately after operation. The INR was checked in the clinic and was 4.7. This patient died before his third clinic appointment. No hyphaemas followed cataract surgery in the diabetics and none in the three cases where corneal sections were used.

Discussion

If anticoagulation is not discontinued, it is not known at what level of INR the risk of ocular complications is reduced without putting the patient at risk of

Table 1 *Reasons for anticoagulation*

Femoral embolus, aortic valve replacement, coronary artery bypass
Mitral valve replacement
Mitral valvotomy, homonymous hemianopia
Arterial thrombosis (leg)
Atrial fibrillation, embolic transient ischaemic attack
Deep vein thrombosis
Mixed aortic and mitral valve disease
Mixed mitral valve disease

Table 2 *Range of BCR/INR*

BCR/INR	Number of patients
1.5-2.4	5
2.5-3.4	4
3.5-4.4	0
4.5	1

BCR=British comparative ratio. INR=international normalised ratio.

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embolism or thrombosis. Four of our patients were not fit for general anaesthetic, and the risk of retrobulbar haemorrhage with local anaesthesia was a very real consideration.

The British Society for Haematology recommended therapeutic ranges for BCR/INR¹ are: 2.0 to 3.0 for the treatment of deep vein thrombosis (DVT), pulmonary embolism, and transient ischaemic attack (TIA); 3.0 to 4.5 for recurrent DVT and pulmonary embolus (PE), and arterial disease including cardiac prosthetic valves and grafts.

In a survey of 135 members of the American Intraocular Implant Society by Stone *et al.*² 75% withheld warfarin prior to and following surgery. Twenty-two instances of ocular complications including hyphaema, conjunctival/incisional bleeding, retrobulbar haemorrhage, retinal haemorrhage, and expulsive haemorrhage were reported. None of the 10 ophthalmologists who continued anticoagulation listed any adverse effects. Systemic complications attributed to withholding anticoagulation included death from cerebrovascular accident, TIA, revision of coronary bypass graft, cerebral embolism in a patient with an artificial heart valve, PE and DVT. Some ophthalmologists gave platelets, vitamin K, heparin, and fresh frozen plasma preoperatively.

Hall *et al.*³ contend that anticoagulants which are necessary to control a life threatening process should not be terminated before intraocular surgery. In their most recent series of 49 cataract operations⁴ all were performed under local anaesthesia. Most of the patients underwent a peripheral iridectomy. Eighteen of the operations were intracapsular extractions, 11 with medallion intraocular lenses, and 30 were extracapsular extractions with posterior chamber intraocular lenses. Prothrombin times were 1.5 to twice normal in 20 patients, were normal in 11, and between normal and 1.5 times normal in 18. Three hyphaemas occurred, and two patients died within six months of surgery.

In our 10 patients three hyphaemas occurred. Two were mild and did not adversely change the final outcome. The third hyphaema appeared some time

postoperatively and was associated with a rise in INR from 3.1 to 4.7. It should be remembered that the INR may increase if additional drugs such as prophylactic antibiotics are given, but no additional drugs were given in this particular case.

Spontaneous hyphaema has been described as a result of warfarin therapy.⁵ Maida has reported three anticoagulated patients with iris clip lenses who developed microhyphaemas some months postoperatively.⁶

Surgical technique may be modified to reduce the risk of bleeding, for example, a corneal section, avoiding an iridectomy or iris suture, careful cautery, the use of sodium hyaluronate, and an endocapsular technique placing loops into the capsular bag to prevent erosion of the loops into the ciliary sulcus. Local anaesthesia could also be modified, for example without retrobulbar injection,⁷ to reduce the risk of bleeding.

Cataract surgery can be performed successfully without discontinuing warfarin. It would seem reasonable to reduce the warfarin before surgery until the INR is just within the recommended therapeutic range and to keep a careful check of the INR in the postoperative period if additional drugs are given.

We thank Mr P A Graham, Mr P V Mills, Mr J W Hunter, and Mrs L Beck for permission to include their patients in this study.

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Results of penetrating keratoplasty for pseudophakic bullous keratopathy with the exchange of an intraocular lens

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SUMMARY We report on 29 consecutive patients with pseudophakic bullous keratopathy who underwent in one eye penetrating keratoplasty with an exchange of the original intraocular lens for a Pearce tripod posterior chamber lens, and who were available for a follow up of at least 12 months. The average interval between cataract extraction with lens implantation and the appearance of bullous keratopathy was five and a half years (range 10 months to 16 years). The mean follow-up period after penetrating keratoplasty was 36 months (range 12 to 56 months). The corneal graft remained clear in 22 (76%) eyes. One year after the operation 45% of the eyes had a vision of 20/40 or better, and 20% had visual acuities between 20/40 and 20/100. The remaining 31% had a vision of 20/100 or less (one unknown). Nine eyes (31%) had cystoid macular oedema or macular degeneration. 45% of the eyes had a refraction within approximately 2 dioptres of emmetropia. In patients with pseudophakic corneal oedema we continue to exchange the intraocular lens by a Pearce tripod posterior chamber lens sutured to the iris when it is necessary to remove the lens.

Pseudophakic corneal oedema is now the most common indication for penetrating keratoplasty in the United States.¹⁻⁴ Patients who underwent cataract extraction with implantation of an iris supported intraocular lens (IOL) still form the largest group of patients undergoing penetrating keratoplasty in The Netherlands.

Several authors have previously reported the results of keratoplasty in patients with pseudophakic bullous keratopathy from whom the intraocular lens was removed, retained, or exchanged.

Before 1980 we removed or retained and fixated the iris supported IOLs to the iris, the decision depending on the decentration or movements of the IOL, erosive iris atrophy, and other pathological states of the eye. We found that after removing the IOL many elderly monocular aphakes could be fitted with a contact lens, but that they discontinued use of the lens after some time despite good vision. We therefore began exchanging the iris supported intra-

ocular lens in the anterior chamber, at first, for a Pearce bipod posterior chamber lens and then, from 1982 on, with a Pearce tripod posterior chamber lens sutured to the iris when it was necessary to remove the iris supported IOL. If the intraocular lens was well fixated and well positioned in the eye, particularly after an extracapsular lens extraction, and in our opinion not the cause of the corneal oedema, we left the lens in place.

In this study we evaluate our results of penetrating keratoplasty for pseudophakic bullous keratopathy with exchange of intraocular lens using a Pearce tripod posterior chamber lens sutured to the posterior iris.

Patients and methods

We studied retrospectively the clinical records of 32 consecutive patients with pseudophakic bullous keratopathy who between January 1982 and May 1986 underwent a penetrating keratoplasty with exchange of intraocular lenses by a Pearce tripod posterior

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chamber lens. All eyes had moderate to severe irreversible corneal oedema with or without bullae. The intraocular pressure was within normal limits before surgery, though six eyes needed medication for glaucoma. One eye had cystoid macular oedema before the operation, proved by fluorescein angiography. If the retina could not be examined with the ophthalmoscope before the operation, an electroretinogram (ERG) was made, and the visually evoked potentials (VEP) measured. All patients were operated on by one of the three corneal surgeons in the Rotterdam Eye Hospital, all three using the same technique. Of these patients 62% were women, ranging in age from 57 to 92 years, mean 78 years. The age of the men ranged from 45 to 87 years, mean 72 years. Three patients were unavailable for follow-up of at least 12 months. Two patients died, and one patient was unavailable for follow-up. We report on the remaining 29 patients whose cases were followed up after surgery for a period of 12 to 56 months, mean 36 months.

SURGICAL TECHNIQUE

The pupil was neither constricted nor dilated before surgery with the patient under general or local anaesthesia. A single Flieringa ring was sutured to the episclera with six 7-0 silk sutures. Gentamicin 0.5 ml was administered subconjunctivally outside the ring. Trephination was performed with a free trephine blade without handle or obturator.^{7,8} The diameter of the trephine blade ranged from 7.0 to 8.5 mm. A diameter of 7.5 and 8.0 mm was used in, respectively, 34% and 45% of the eyes. The iris supported IOL was removed and an anterior vitrectomy was done with cellulose sponges and scissors if there was a prolapse of the vitreous into the pupil or incarceration of vitreous in the cataract wound (13 eyes). In some eyes haptics were amputated first and adhesions between iris, vitreous, and IOL were dissected. This was done carefully with the least possible trauma to the ocular structures.

At the same time the assisting surgeon knotted a single armed 10-0 prolene suture to each of the three holes of the iris stitch Pearce tripod lens with 10-15 knots leaving a small loop of the prolene suture through the hole of the lens⁹ (Fig. 1). This allows a tolerance for a slightly misplaced suture and prevents pulling of the knot through the iris. The lens was placed on the peripheral corneal rim and the two sutures, tied to the inferior holes of the lens, were passed through the pupil and from posteriorly through the iris half way between pupil and the angle. Then the IOL was placed behind the iris, and, if necessary, iridoplasty was performed with a 10-0 polypropylene suture. The 12 o'clock fixation suture was passed through the pupil and from posteriorly through the

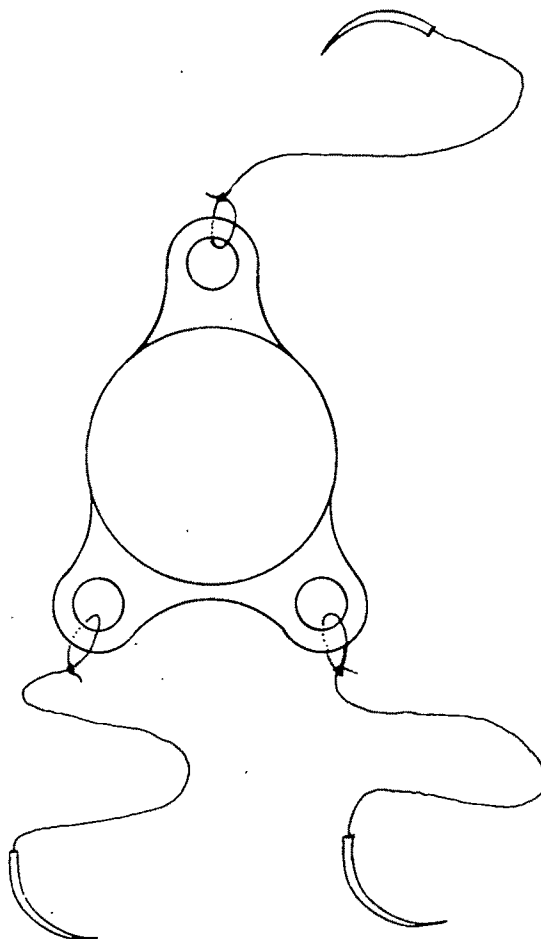


Fig. 1 Pearce tripod lens with three prolene sutures knotted to the holes of the lens.

iris, and the three sutures were pulled gently to check if the lens was properly placed. The sutures were fixed to the iris with a second pass through the anterior surface of the iris, and then secured with a knot.

Initially the power of the tripod lens was calculated with the Binkhorst formula from axial length measurement of the pseudophakic eye and keratometry of the other eye. After myopic surprises we started using the average postoperative keratometry readings from the previous series of penetrating keratoplasties for pseudophakic and aphakic corneal oedema.¹⁰

Donor tissue stored in McCarey-Kaufman medium was used within 48 hours of preservation. A new disposable razor blade trephine, 0.5 mm larger in diameter than the host trephine, was used to punch out the donor button from the endothelial side of the

cornea on a Teflon block.¹¹ Before 1983 the donor corneal button was then sutured to the host cornea with a single running 10-0. From 1983 it was sutured with eight interrupted 10-0 and a running 11-0 nylon suture.¹² At the end of the procedure a subconjunctival injection of soluble corticosteroid was given.

After surgery antibiotics and tapering doses of topical corticosteroids were administered, with most patients being maintained on a regimen of a daily dose of one drop of dexamethasone 0.1%.

Results

The interval between and the implantation of the first intraocular lens after lens extraction and the first appearance of bullous keratopathy ranged from 10 months to 16 years, mean 5½ years (SD 4.5 years). In all patients the first intraocular lens was an iris supported lens, implanted after an intracapsular cataract extraction in 59% and after an extracapsular extraction in 41% of the cases. The criteria for removal of the intraocular lens are specified in Table 1.

Complications immediately after operation were a mild hyphaema (one eye), vitreous prolapse in the

Table 1 Indication for removal, and type of intraocular lens removed, during penetrating keratoplasty in 29 eyes with pseudophakic corneal oedema.

	Intracapsular cataract extraction (n=17)		Extracapsular cataract extraction (n=12)	
	Binkhorst 4 loop	Worst medallion	Binkhorst 2 loop	
Malposition	4	2	7	(45%)
Endothelium touch	1	3	1	(17%)
Excess lens movements	2	1		(10%)
Retrolental membrane		1		(3%)
Not specified	2	1	4	(24%)
Total number	9	8	12	

Table 2 Postoperative complications after penetrating keratoplasty with exchange of the intraocular lens

Late complications*	No.
Cloudy cornea	7
Cystoid macular oedema	3
Macular degeneration	6
Partly dehiscent graft	2
Posterior capsule haze	1
Persistent postoperative pain	1
Retinal detachment	1

*Frequently more than one complication in one eye.

CORNEAL GRAFT SURVIVAL IN %

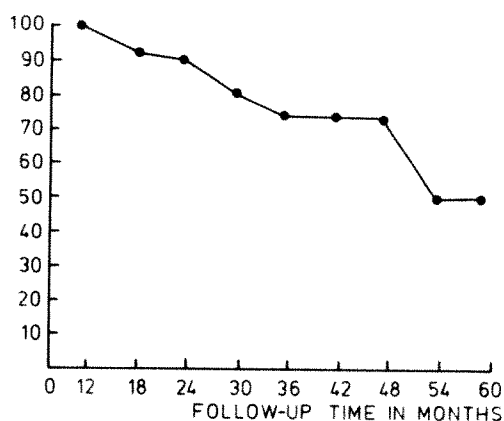


Fig. 2 Corneal graft survival curve after penetrating keratoplasty with an exchange of the intraocular lens.

anterior chamber (one eye), and slow re-epithelialisation of the cornea (two eyes). There were no cases of primary graft failure. Long-term complications are summarised in Table 2.

One patient developed a persistent corneal ulcer eight months after keratoplasty, and the cornea was covered with a conjunctival flap.¹³ Apart from this patient all other corneal transplants remained clear during the first 12 months of the follow-up period. The graft survival curve is shown in Fig. 2. After an average of 29 months (range 16 to 54 months, SD 13 months) seven grafts (24%) opacified. Three grafts opacified owing to an irreversible graft rejection and two slowly opacified without obvious reason. One patient developed a silicone oil keratopathy due to silicone oil in the anterior chamber after a retinal detachment.¹⁴ In one patient with severe persistent postoperative pain and cystoid macular oedema the clear graft and the still oedematous peripheral rim of the recipient cornea were covered with conjunctiva.¹⁵

The visual acuities after the operations are shown in Table 3. Of the 15 eyes that did not achieve a visual

Table 3 Visual acuity after penetrating keratoplasty with intraocular lens exchange

Visual acuity	20/40 or more	20/40 -20/100	20/100 or less	Unknown
One year postoperative	13 (45%)	6 (20%)	9 (31%)	1 (3%)
Most recent	12 (41%)	4 (14%)	11 (38%)	2 (7%)
Best postoperative ever	17 (58%)	4 (14%)	8 (28%)	-

acuity of 20/40 or more three had cystoid macular oedema, one eye had a conjunctival flap, and six had macular abnormalities. In five eyes the reasons for poor visual acuities remained unknown or were not mentioned in the clinical records.

There was no difference in visual acuity between the eyes in which an anterior vitrectomy was performed during keratoplasty and those without vitrectomy.

The mean spherical equivalent of the most recent refraction was -2.4 dioptres (range $+3$ to -10 , SD 4.1). 45% of the eyes had a refraction within approximately 2.0 dioptres of emmetropia. Corneal astigmatism, measured one year after operation, showed a mean of 5.6 dioptres (range 1 to 8, SD 3.9). The mean keratometry one year after keratoplasty was 48 dioptres (range 42.7 to 52.5 dioptres). Because most eyes still had some of the interrupted 10-0 nylon corneal sutures in place at the time these measurements were taken, the refractions and visual acuities may differ when all sutures are removed.

Six eyes with raised intraocular pressure were controlled medically before the operation. Intraocular pressure was raised in 13 eyes (46%) after the keratoplasty. Eight of these eyes (66%) had a visual acuity of 20/40 or better. In two eyes the intraocular pressure, which was too high before operation, was normal after keratoplasty. Two eyes with a raised intraocular pressure had paracentral scotoma. In only one eye could the pressure not be controlled with medication and we therefore performed cyclo-cryocoagulation.

Discussion

Our results show that pseudophakic corneal oedema appeared on an average $5\frac{1}{2}$ years after cataract extraction, SD $4\frac{1}{2}$ years. Other authors mention an average period between five months and $4\frac{1}{2}$ years.^{2,3,5,6}

In The Netherlands intraocular lenses have been implanted for more than 20 years. In some cases corneal oedema appears long after the operation has taken place. In one case the pseudophakic corneal oedema appeared after 16 years. This may explain the longer time lapse from lens implantation to onset of corneal oedema found in our study.

Of the grafts reported on here 97% remained clear during the first 12 months. Later seven grafts (24%) opacified. Five of these showed pseudophakic corneal oedema, which occurred an average of 29 months after the keratoplasty. Other studies have reported the development of pseudophakic corneal oedema in the graft in 9 to 20% of cases, with a mean follow-up of less than two years (Tables 4, 5). As several authors have shown that, following kerato-

plasty for pseudophakic bullous keratopathy, a progressive loss of endothelial cells occurs, it is most likely that the number of eyes with corneal decompensation will increase with a longer follow-up period.¹⁵ The mean follow-up period in our study was 36 months, SD 14 months.

All patients had an iris supported intraocular lens implanted, and the main complication we found was malposition and excessive movement of the lens, which resulted in a bullous keratopathy and low visual acuity. In some cases the appearance of bullous keratopathy may have been due to chronic low-grade uveitis.¹⁶

Before 1980 we removed or retained and fixed the iris supported IOLs to the iris, depending on the decentration or movements of the IOL, iris atrophy, the uveitis-glaucoma-hyphaema syndrome and other pathology of the eye. This was a very controversial subject at that time, and other studies were difficult to compare with ours because the study population and surgical technique varied, and the criteria for retention or removal were not specified. Some surgeons removed all implants, while others tried to retain them when possible. Without sodium hyaluronate it was technically difficult safely to suture the donor button over an iris supported implant. We started first to exchange the iris supported intraocular lens in the anterior chamber for a Pearce bipod posterior chamber lens and from 1982 on, for a

Table 4 Results after penetrating keratoplasty for pseudophakic bullous keratopathy

Author	No. of eyes	Follow-up (months)	IOL removal	Clear grafts
Taylor <i>et al.</i> ²	42	1-51 (mean 14.8)	7/42	88%
Waring <i>et al.</i> ¹	25	12-38 (mean 18.7)	25/25 exchanged	88%
Waring <i>et al.</i> ³	35	? (mean 14.8)	35/35	91%
Meyer and Sugar. ⁵	25	6-41 (mean 20)	11/25	88%
vd Schaft <i>et al.</i>	29	12-56 (mean 36)	All exchanged	83%

Table 5 Results after penetrating keratoplasty for pseudophakic bullous keratopathy

Corneal macular oedema	Macular degeneration	VA 20/40 or more	VA 20/40 -20/100	VA 20/100 or less
6%	11%	32%	19%	49%
37.5%	12%	36%	46%	18%
43%		17%	60%	23%
24%	8%	52%	16%	32%
10%	21%	41%	14%	38%

Pearce tripod lens sutured to the iris, when it was necessary to remove the iris supported lens.¹⁶ A lens in the posterior chamber sutured to the iris made it much easier to suture the donor button in the recipient cornea safely. Sodium hyaluronate has made surgery less complicated, but does not change the indications for retaining or exchanging an intraocular lens. The lens is retained if properly fixed in the eye and if not affected by intraocular inflammation.

There were few intra- and postoperative complications, and the longer term complications were mainly bullous keratopathy (17%), macular degenerations (20%), and cystoid macular oedema (10%). It was not known whether the last two complications existed before the operation (Table 2). Corneal oedema frequently makes preoperative examination of the retina difficult.

Visual acuity (Table 3) after keratoplasty and lens exchange improved in 65%, and in 31% there was no improvement. We always inform our patients carefully that macular disease may be present.¹⁷

It was difficult in our study to demonstrate a strong correlation between the development of cystoid macular oedema and anterior vitrectomy during operation, though other authors have suggested or demonstrated that anterior vitrectomy induces it to develop.¹⁸

There was no correlation between a postoperative high intraocular pressure and the visual outcome, though two eyes developed paracentral scotoma. A raised intraocular pressure was not a rare complication, but in all but one eye it was successfully lowered with medication. The incidence of postoperative raised intraocular pressure might be reduced by performing goniotomy during penetrating keratoplasty.⁴

In our study the earliest postoperative refraction was within the range of 2 dioptres of emmetropia in only 45% of the eyes.

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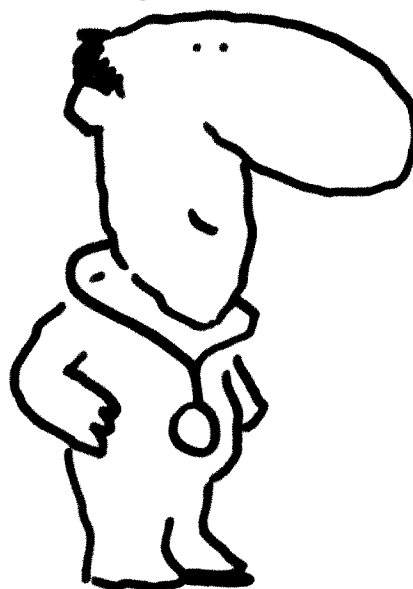
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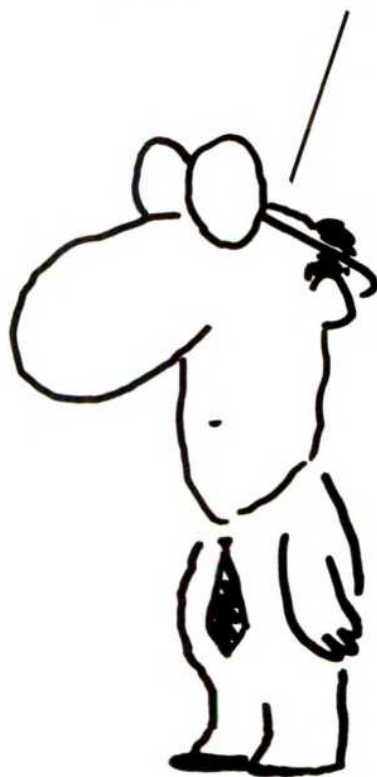
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Intraocular lens power calculations in the triple procedure

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SUMMARY When a triple procedure is planned, calculation of the intraocular lens becomes a problem. Postoperative corneal power bears no relation to preoperative power, and the axial length of the globe also changes. A prospective study of 24 keratoplasties revealed a close relationship between postoperative corneal power and donor corneal power. Changes in axial length were found to be too small to produce errors in calculation. The equation derived in this series to describe the relation between postoperative and donor corneal power is applicable only when certain trephine sizes are used and when the recipient cornea is not excessively scarred.

When a corneal opacity and cataract coexist, the triple procedure—namely, keratoplasty, cataract extraction, and intraocular lens implantation—becomes one of the options a surgeon has to consider. Its main advantage is more rapid visual rehabilitation than that resulting from multiple-step treatment. Proper calculation of lens power depends on the accurate measurement of corneal power (K) and axial length (L) preoperatively.¹ In the triple procedure the postoperative changes in K and L induced by keratoplasty may be a major source of error in lens power selection. Some surgeons use the preoperative K of the operated or fellow eye in their formulae.² Others use average K values derived from their own series³ on the assumption that there is no correlation between pre- and postoperative K values.

In this prospective study readings obtained from 24 keratoplasties are analysed. The trephine diameters were the same at each operation. A 7.5 mm trephine was used to obtain the donor button and a 7 mm trephine to cut the recipient bed. The same surgical technique was followed by a single surgeon in all 24 cases. Pre- and postoperative K and L readings were recorded as well as 'donor K'. A mathematical model has been constructed to explain the relation between

donor K and final postoperative K. Another model was set up to calculate changes in L after surgery.

Material and methods

Twenty-four eyes with weak vision due to corneal opacification were selected. Table 1 shows the pathology in them. Eight patients were female and 16 male. Their ages ranged from 16 to 52 years.

PREOPERATIVE MEASUREMENTS

The recipient eye. (a) Corneal power was measured with the Haag-Streit model keratometer. In case of astigmatism, the average K was recorded. (b) Ultrasonic axial length (L) was measured in mm with the Cooper vision imaging machine. L was measured in seven cases only.

The donor globe. K in the donor globe was measured as follows. Fresh donor globes were obtained within six hours of death. Under strict sterile conditions Ringer-lactate solution was injected into the vitreous chamber with a 25 G needle introduced 10 to 12 mm behind the limbus obliquely through the sclera and pointing towards the centre of the globe. Enough solution was injected until the globe was felt to become firm. The needle was then removed and the globe pressure was checked by an applanation tonometer. The globe was held by one of

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Table 1 The corneal pathological states in the recipient eyes

Pathology	No. of eyes	Percentage
Leucoma	12	50
Keratoconus	4	16.7
Dystrophy	4	16.7
Blood staining	2	8.3
Endothelial decompensation	2	8.3

the rectus stumps in front of a Goldmann tonometer. Counter support was applied lightly to the back of the globe by an assistant during measurement. In all globes the pressure was built up to about 15–20 mm Hg. The globe was then held in front of the keratometer and K was measured. The adjacent rectus stump was then held, the globe rotated through 90°, and a perpendicular K measured. The donor K is the average value of these two readings.

OPERATION

The donor button was obtained by a 7.5 mm trephine while the recipient bed was prepared by a 7 mm trephine. The graft was fixed by eight interrupted 10-0 nylon sutures together with a running continuous 10-0 nylon suture. Interrupted sutures were removed four to six months after surgery, the running sutures after 12–18 months.

POSTOPERATIVE MEASUREMENTS

Corneal power. (a) Early K readings were taken two days after surgery. (b) Serial K readings were recorded at monthly intervals up to nine months in all cases.

The axial length was measured in seven of the cases six to eight months postoperatively, when K was found to have become stable.

Results

Fig. 1 shows the distribution of preoperative recipient K measurement, the donor K as well as the early postoperative (two days) and final postoperative (nine months) K values.

Table 2 gives the average values of K (with SD) in each of the above groups. The preoperative K ranged between 32.5 dioptres (D) and 59 D, average 44.82 (7.72) D. The high SD reflects the heterogeneity of this group of readings. Donor Ks were more uniform, lying between 40.5 and 45 D, average 42.39 (1.41) D. Similarly early postoperative Ks were uniform. The average K was 50.53 (1.47) D, lying between 48 and 53 D.

Monthly K measurements showed variations up to six to eight months postoperatively, after which readings became stable. At nine months post-

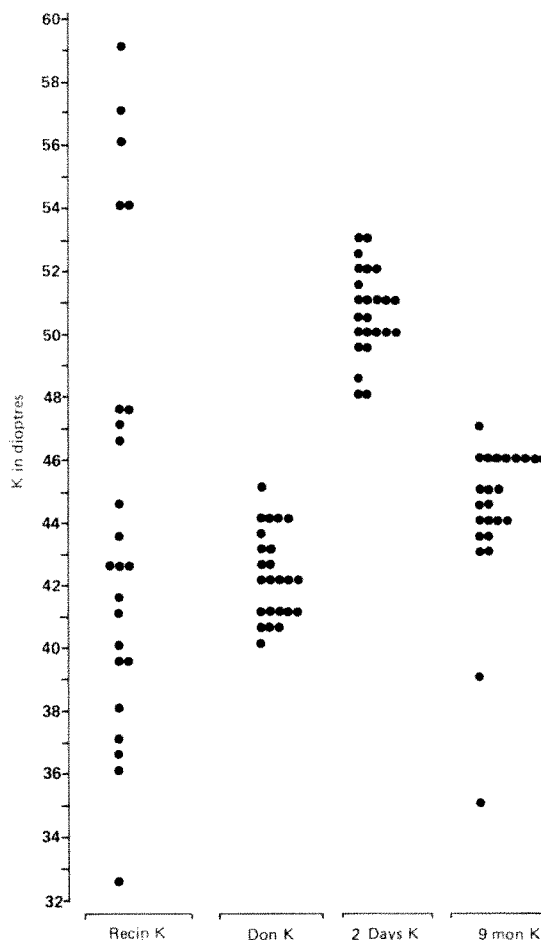


Fig. 1 The distribution of corneal power K in 24 eyes. Recip K = recipient preoperative K. Don K = donor globe K. 2 Days K = 2 days postoperative K. 9 mon K = 9 months postoperative K.

operatively the K readings had an average of 44.05 (2.75) D, range 35 to 47 D. Two particular cases with heavy corneal scarring and vascularisation showed an abnormally excessive postoperative corneal flattening. If these two cases are omitted, the nine months postoperative K average becomes 44.88 (1.23) D.

Table 3 gives preoperative recipient K and L values as well as postoperative K and L values in seven of the cases in this series. It also includes the actual changes in L together with the expected, mathematically calculated changes. Both the actual measurements and the mathematical calculations revealed minute negligible changes in L. Consequently the pre- and postoperative evaluation of L was omitted after the seventh case.

Table 2 Average values of K (with standard deviations) by groups

Group	Average K	Range
Recip preop	44.82 (7.72)	32.5-59
Donor	42.39 (1.41)	40.5-45
Postop 2 days	50.53 (1.47)	48-53
Postop 9 months	44.05 (2.75)	35-47
Postop 9 months after omitting 2 cases	44.88 (1.23)	43-47

Recip preop=corneal power of recipient eyes.

Donor=corneal power of donor recipient eyes.

Postop 2 days=corneal power 2 days after surgery.

Postop 9 months=corneal power 9 months after surgery.

Postop 9 months after omitting 2 cases=above group after omitting 2 cases that showed abnormally excessive corneal scarring.

Average K=mean value of corneal power in dioptres.

Range=range of K in the group.

Discussion

Troutman calculated a 0.67 D increase in K for every 0.1 mm increase of donor button size over recipient bed size.⁴ Casey states that 0.5 mm discrepancy between donor and recipient may reduce hypermetropia by 'a dioptre or two'.⁵ Olson on the other hand reports a statistically insignificant difference between the refraction after same-size grafts and over-size grafts.⁶ This controversy stems from a basic error, which is the attempt to relate preoperative to postoperative corneal powers. As Kozansky and Cavanagh judiciously state, 'there is no relation between the preoperative and postoperative corneal powers'.⁷ The true relation is between the donor K and the postoperative recipient K. After all, it is the donor corneal button that becomes 'squeezed' into a smaller bed with a consequent change in its curvature (K becomes greater).

In Fig. 1 it is obvious how disparate the preoperative K values are. In addition to the different

pathological states involved, this disparity reflects the inaccuracy and difficulty in measuring K in scarred corneas with an irregular surface. Meanwhile donor K values are far more uniform. This is to be expected, since donors are selected on the basis of their 'normal corneas'. Early postoperative K values are similarly rather uniform, though their average value is clearly higher than that of the donors. Nine months later this average value declines considerably, yet uniformity is still preserved.

The first two cases in the study demonstrate this fact clearly. One was a case of keratoconus with an average preoperative K of 57 D, while the other was a case of adherent scar with a K of 36.5 D. Both at the same operative session received grafts from a single donor whose K was 40.5 in both eyes. Their two-day postoperative Ks were remarkably close (48.5 and 49.5 D respectively). A follow-up of corneal powers postoperatively showed a gradual decline for six to eight months before they became stable. Final K values measured nine months after surgery had an average of 44.05 (2.75) D. This matches well with the average postoperative corneal powers reported by several other investigators.^{2,3,8}

Mathematical model

In Fig. 2, if an arc whose length is a , with radius of curvature r_1 and suspended on a chord c_1 , is transferred to another shorter chord c_2 (with $c_1 > c_2$), then the curvature of the arc will become steeper, on the assumption of a new radius r_2 where $r_1 > r_2$:

$$r_1 \sin^{-1} \left(\frac{c_1}{2r_1} \right) = a = r_2 \sin^{-1} \left(\frac{c_2}{2r_2} \right),$$

Where a represents the length of arc of the donor button. Its length depends on:

(1) c_1 , the length of the chord, or in other words the diameter of the trephine used to obtain this button (7.5 mm);

(2) r_1 the radius of curvature of the donor cornea (K value of the donor cornea).

This same button is applied to the recipient bed, prepared by a 7 mm trephine—that is, c_2 becomes 7 mm. It will attain a steeper curvature r_2 . This r_2 , which is the radius of curvature of graft postoperatively, depends on: (1) donor corneal curvature r_1 ; (2) diameter of donor trephine c_1 (7.5 mm); and (3) diameter of recipient trephine c_2 (7 mm).

GRAFT AND RECIPIENT BED RETRACTION

When a donor button of K=42.5 D ($r=7.9$ mm), obtained by a 7.5 mm trephine is fixed into a recipient bed prepared by a 7 mm trephine, the mathematically expected postoperative r would be $r=4.88$ —that is, K>60 D. In practice this did not happen. The two-

Table 3 Preoperative and postoperative K and L values

K preop	K 9mon	L preop	L 9mon	Real diff	Math diff
32.5	35	19.7	19.9	0.2	0.16
46.5	44	24.05	23.9	-0.15	-0.04
36.5	39.5	23.36	23.68	0.32	0.06
42	46	23.87	24	0.13	0.09
43	47	22.6	22.7	0.10	0.06
38	45	22.90	23.2	0.30	0.14
54	39	24.35	23.87	-0.48	-0.165

K preop=preoperative corneal power in dioptres.

K 9mon=postoperative corneal power after 9 months.

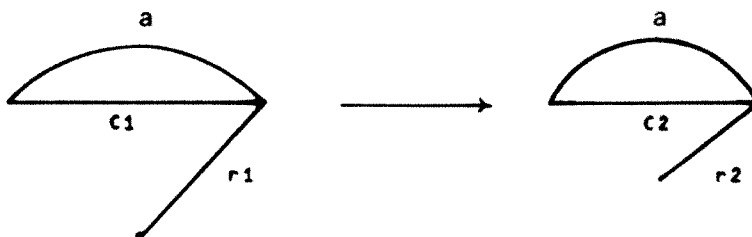
L preop=preoperative axial length in mm.

L 9mon=postoperative axial length after 9 months.

Real diff=measured difference between L 9 months and L preop.

Math diff=mathematically calculated difference.

Fig. 2 The radius of curvature r_1 of the arc a suspended on a chord c_1 changes to r_2 if the length of the chord changes to c_2 , if $c_2 < c_1$, then $r_2 < r_1$ when a is constant.



day postoperative K was found to be $K=50.5$ D. This means that either the recipient bed expanded from 7 mm to 7.36 mm or that the length of arc of the button shrank from 7.81 mm to 7.3 mm. It seems, however, that the bed and button change in size to some extent owing to the retraction of the collagenous corneal stroma when cut. Further changes occurred in graft size and bed width during the first six to eight months following surgery. The corneal power declined gradually to reach a steady state — 'final corneal power' — thereafter.

EXCESSIVE CORNEAL SCARRING

In corneas with heavy scarring the postoperative flattening was noticed to be excessive. Two cases in this series suffered in this way: the postoperative K dropped from 50 D and 52.75 D, two days after surgery, to 35 D and 39 D after nine months. Measurement of the graft-bed interface at nine months showed an increase from 7 mm to 7.6 and 7.8 mm respectively. The recipient bed in scarred corneas seems to be liable to abnormal degrees of shrinkage, leading to unexpectedly low final K values.

RELATION BETWEEN 'DONOR K' AND 'FINAL POSTOPERATIVE K'

After omission of the two cases with excessive corneal scarring the average final postoperative K becomes 44.88. That is to say:

When a 7.5 mm corneal button obtained from a donor globe with a corneal power K_1 is applied to a recipient bed of 7 mm diameter, the expected final postoperative corneal power after nine months can be predicted from the equation:

$$K_2 = K_1 + 6\% K_1.$$

AXIAL LENGTH CHANGES

Theoretically, any change in corneal curvature is expected to result in an associated change in axial length $*L$ where:

$$*L = (2r_2 - \sqrt{4r_2^2 - c_2^2}) - (2r_1 - \sqrt{4r_1^2 - c_1^2})$$

In seven cases $*L$ was actually measured and mathematically calculated as well. In all seven cases $*L$, both by measurement and by calculation, proved to be negligibly small (Table 3). The preoperative axial length can safely be applied in the IOL calculations formula.

CONCLUSION

In calculating the IOL power P in eyes with an axial length between 22 mm and 24 mm the most commonly accepted formula is the SRK linear regression formula.⁹

$$P = A - 2.5L - 0.9K,$$

where A is the lens constant specific to the type of lens.

If the axial length is <22 mm or >24 mm, a modified SRK II formula is applied.⁹ In the former condition $+1$ is added to the A constant, while in the latter condition -1 , or -2 is added to A .

In the triple procedure both the SRK and the SRK II linear regression formulae may be used after some necessary changes: L is the preoperative axial length of the operated eye; but K may be either (a) 106% the donor K , or (b) an arbitrary value of 45 D if the donor K is not available.

It must be stressed, however, that the above statement is applicable only if (1) a 7.5 mm graft is placed in a 7 mm bed, and (2) the recipient bed is not heavily scarred. In this latter situation such eyes may benefit more by undergoing two separate surgical procedures: a penetrating keratoplasty and extracapsular cataract extraction followed later by a posterior chamber IOL after postoperative K values have stabilised.¹⁰

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A point prevalence study of 150 patients with idiopathic retinal vasculitis: 1. Diagnostic value of ophthalmological features

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SUMMARY This paper describes the ophthalmological features of 150 patients with idiopathic retinal vasculitis, 67 of whom had isolated retinal vasculitis (RV) and 83 had RV associated with systemic inflammatory disease (RV+SID). The diagnosis of retinal vasculitis was made by ophthalmoscopy and fluorescein angiography, and patients with any identifiable cause (infection, ischaemia, or malignancy) were excluded from the study. Patients with isolated RV tended to have peripheral vascular sheathing, macular oedema, and diffuse capillary leakage. Those with RV accompanying Behçet's disease often had branch vein retinal occlusions and retinal infiltrates together with macular oedema and diffuse capillary leakage; the retinal infiltrates were pathognomonic for Behçet's disease. In sarcoidosis the retina typically showed features of periphlebitis associated with focal vascular leakage. Patients with uveomeningitis, multiple sclerosis, arthritis, or systemic vasculitis showed diffuse retinal capillary leakage associated with a mixture of the other features. Poor visual function was particularly associated with macular oedema and branch vein retinal occlusion, while the retina appeared to 'withstand' the impact of vascular sheathing, periphlebitis, or neovascularisation alone. Within the limitations of a point prevalence study it was concluded that different patterns of retinal vasculitis occur in different systemic inflammatory diseases, and that in isolated retinal vasculitis there is a particular association between peripheral vascular sheathing, macular oedema, and diffuse capillary leakage. In Part 2 we describe the results of examining the sera of these patients for the presence of antiretinal antibodies and circulating immune complexes.

Retinal vasculitis is a sight-threatening inflammatory eye disease whose aetiology and pathogenesis remain obscure. It may occur as a complication of infective, neoplastic, or degenerative disorders, in association with systemic inflammatory diseases (for example Behçet's, sarcoidosis) or as an isolated phenomenon. The ophthalmological features consist of cells in the vitreous accompanied by involvement of retinal vessels: the retinal veins are most commonly affected, and sheathing of the postcapillary venules frequently

occurs together with evidence of diffuse capillary leakage on fluorescein angiography. As the retinal capillaries are frequently involved, there is loss of integrity of tight junctions between capillary endothelial cells which results in macular oedema and consequently visual loss. In contrast the retinal arterioles are rarely affected, except in advanced cases, where arteriolar occlusion is characteristically accompanied by multiple retinal vein occlusions.

The ophthalmological features of retinal vasculitis which occur in viral,^{1,2} parasitic,³ or fungal disease⁴ are easily recognised, as are those of an ischaemic or neoplastic nature,^{5,6} where examination of the eye

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frequently provides information relevant to the clinical diagnosis of the underlying general medical disorder.

However, when retinal vasculitis accompanies systemic inflammatory disease, or occurs as an isolated phenomenon, the ophthalmological features appear to be less discriminatory. This study of 150 patients with retinal vasculitis was carried out primarily to determine whether any ophthalmological features could discriminate between patients with isolated retinal vasculitis (RV) and those with retinal vasculitis accompanying systemic inflammatory disease (RV+SID). A second objective was to determine whether any such ophthalmological features had predictive significance in terms of visual outcome.

Patients and methods

The patients were selected from those attending the Medical Eye Unit and the Inflammatory Eye Disease Clinic at St Thomas's Hospital. The majority were referred from hospitals elsewhere, but a few attended the Casualty Department. The diagnosis of retinal vasculitis was made on the ophthalmoscopic criterion of cells in the vitreous in association with involvement of retinal vessels (by ophthalmoscopy and/or fluorescein angiography). Patients with retinal vasculitis due to an identifiable cause (infection, ischaemia, or malignancy) were excluded from the study.

All patients had a full ophthalmological assessment by at least two observers. This included visual acuity corrected for distance and near, colour vision, and slit-lamp examination. The eyes were dilated in all patients and examined by indirect and direct ophthalmoscopy and a fundus lens. Colour fundus photography and fluorescein angiography were undertaken in most cases. Peripheral vascular sheathing was defined as sheathing of retinal vessels, whether or not associated with fluorescein leakage; sheathing was often seen in the peripheral retina where it was difficult to record photographically. Periphlebitis was defined as focal fluffy white cuffing of retinal veins; this occurred in association with focal leakage of fluorescein at these sites of inflammation.

The severity of the ocular inflammation in each patient was assessed by means of a points system previously described,⁷ and each patient was thereby allocated an ocular disease score. All patients had a full general medical examination and most had a chest x-ray and a Mantoux test. Systemic inflammatory diseases were identified by standard clinical criteria in Behçet's disease⁸ and systemic lupus erythematosus⁹ as well as by histological examination of lung or skin biopsies in sarcoidosis.

Table 1 Ophthalmological features of 67 patients with isolated retinal vasculitis

Feature	No. of patients
Anterior uveitis	23 (33%)
Macular oedema	40 (60%)
Peripheral vascular sheathing	43 (64%)
Periphlebitis	10 (15%)
Retinal vein occlusion	6 (9%)
Retinal neovascularisation	11 (16%)
Retinal infiltrates	0 (0%)
Pigment epithelial disease	22 (33%)

ASSEMBLY AND STATISTICAL ANALYSIS OF RESULTS

Details of all patients were entered on to a proforma. Statistical analysis was performed by χ^2 tests and 95% confidence limits.

Results

One hundred and fifty patients fulfilled the criteria of retinal vasculitis for entry into the study. Two-thirds of the patients were under 40 years of age; 71 (47%) were male and 79 (53%) female. Sixty-seven patients had isolated retinal vasculitis (RV) and 83 had retinal vasculitis in association with systemic inflammatory disease (RV+SID).

FEATURES OF 67 PATIENTS WITH ISOLATED RV

Twenty-seven patients in this group were male and 40 were female, and 72% of them were aged between 15 and 40 years. The ophthalmological features are sum-

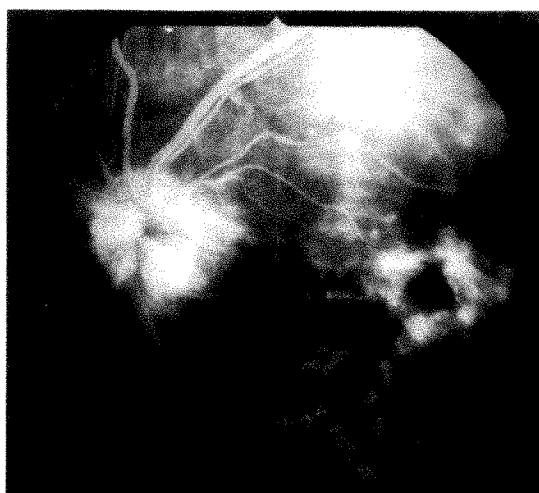


Fig. 1 Fluorescein angiogram in arteriovenous phase of left eye in 23-year-old girl with a two-year history of floaters and poor central vision.

Table 2 Findings on fluorescein angiography in patients with isolated retinal vasculitis and retinal vasculitis associated with sarcoidosis and Behçet's disease

	Isolated RV (60 patients)	RV+ Behçet's (29 patients)	RV+ sarcoidosis (14 patients)
Capillary leakage	47 (78%)	29 (100%)	6 (43%)
Capillary closure	14 (23%)	14 (48%)	2 (14%)

marised in Table 1. The most prevalent findings were sheathing of peripheral retinal vessels, found in almost two-thirds of patients, and macular oedema, found in 60% (Fig. 1). One-third of the patients had atrophic pigment epithelial lesions. Retinal neo-vascularisation was observed in 13 patients (16%) but was associated with retinal ischaemia in only five. Fluorescein angiography showed that, whereas the majority of patients had diffuse capillary leakage, only a quarter had capillary closure (Table 2). Thirty-two patients had mild or moderate disease with a score of 10 or less, and 35 had pronounced or severe disease. These 67 patients generally retained good vision: two-thirds had a visual acuity of 6/18 or better in at least one eye and only 22% had a visual acuity of worse than 6/18 in both eyes.

FEATURES OF 83 PATIENTS WITH RV+SID

Forty-four patients in this group were male and 39 were female, and 61% of them were aged between 15 and 40 years. Thirty-nine patients had Behçet's disease, 17 had sarcoidosis, 11 presented with a uveomeningitic illness, nine had seronegative arthritis (in five, associated with HLA B27), two had systemic lupus erythematosus, two had glomerulonephritis, and three had polyarteritis nodosa, Crohn's disease, and Wegener's granulomatosis respectively.

In these patients a clinical diagnosis of systemic inflammatory disease (SID) was made after a full general history and examination, and laboratory investigations were confirmatory. Laboratory inves-

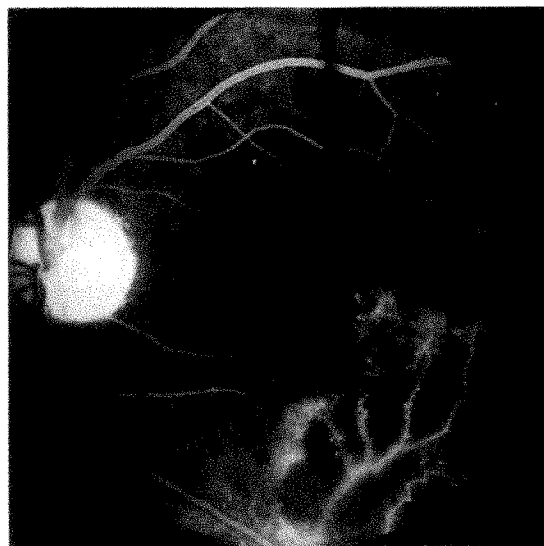


Fig. 2 Fluorescein angiogram of only eye of 35-year-old Caucasian with Behçet's disease with a one-week history of sudden loss of vision. The inferotemporal vein is irregular, tortuous, and dilated with staining of fluorescein. Macular oedema, capillary dilatation, and capillary closure are present in the affected quadrant.

tigations never revealed a systemic inflammatory disease in the absence of clinical signs.

The ophthalmological features differed according to the nature of the systemic inflammatory disease (Tables 2, 3).

BEHÇET'S DISEASE (39 PATIENTS)

In this group 26 patients were male and 13 were female, and two-thirds were under 40 years of age. Twenty-eight patients were Anglo-Saxon, and there were also five patients from the Middle East, three Mongolian Asians, two West Indians and one Indian Asian. All 39 patients suffered with mouth ulcers and 29 (74%) also had genital ulcers; in addition 18 (46%)

Table 3 Ophthalmological features of patients with retinal vasculitis associated with Behçet's disease, sarcoidosis, uveomeningitic syndrome and HLA B27-related arthritis

	Behçet's (39 patients)	Sarcoidosis (17 patients)	Uveomeningitic syndrome (11 patients)	HLA B27-related arthritis (5 patients)
Anterior uveitis	19 (49%)	7 (41%)	4 (36%)	5 (100%)
Macular oedema	26 (67%)	6 (35%)	8 (73%)	4 (89%)
Peripheral vascular sheathing	14 (36%)	3 (18%)	5 (45%)	0
Periphebitis	9 (23%)	11 (65%)	3 (27%)	0
Retinal vein occlusion	20 (51%)	2 (12%)	2 (18%)	0
Neovascularisation	6 (15%)	3 (18%)	3 (27%)	0
Retinal infiltrates	13 (33%)	0	0	0
Pigment epithelial disease	8 (21%)	5 (29%)	1 (9%)	0

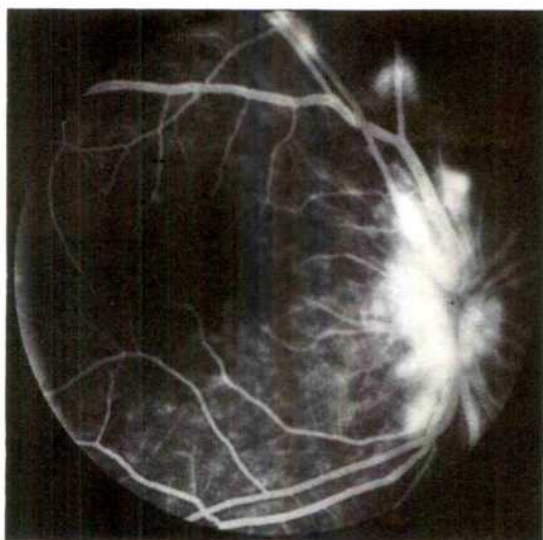


Fig. 3 A 20-year-old lad from Hong Kong presented with bilateral vitreous haemorrhages. He had new vessels on both optic discs, and fluorescein angiography did not show any associated capillary closure.

had arthritis, 20 (51%) skin rashes, and 17 (44%) thrombophlebitis. Seven patients (18%) had central nervous system involvement, which was usually of the brain stem but also included optic neuritis and benign intracranial hypertension.

The most prevalent ophthalmological features

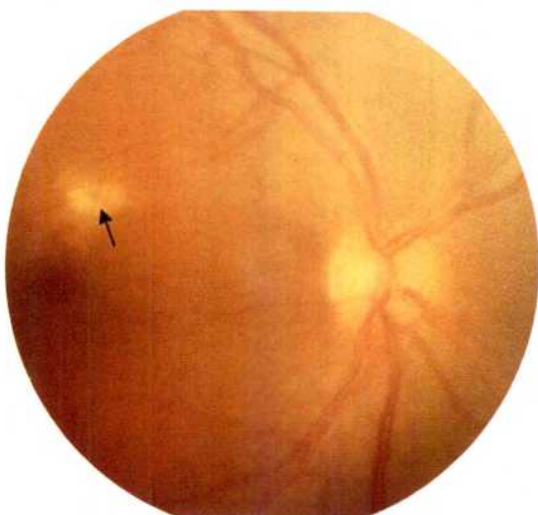


Fig. 4 The right fundus of a young Pakistani with Behçet's disease and active arthritis and orogenital ulceration. The view is poor due to vitreous haze. A retinal infiltrate (arrow) is present just above the fovea obscuring the vascular outlines.

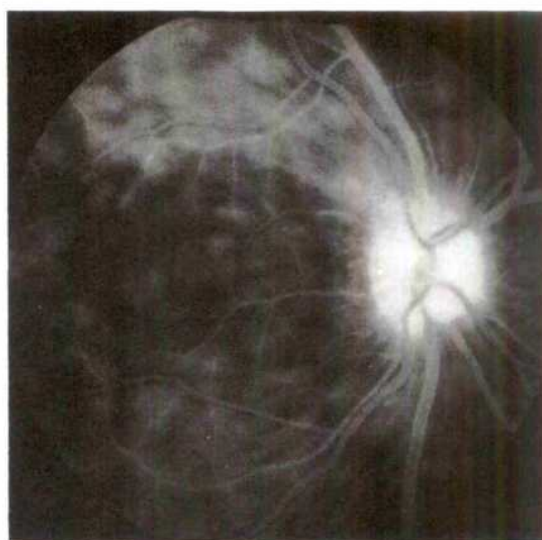


Fig. 5 Anteriovenous phase of fluorescein angiogram of right eye of young man with Behçet's disease. There is diffuse capillary leakage throughout the posterior pole.

were the presence of branch retinal vein occlusions, retinal infiltrates, and diffuse capillary leakage. Branch retinal vein occlusion occurred in 25 patients (64%) (Fig. 2), and three of these subsequently acquired retinal new vessels. New vessels occurred in three other patients, during active inflammation, but in the absence of capillary closure (Fig. 3). Retinal infiltrates occurred in 13 patients (33%). These

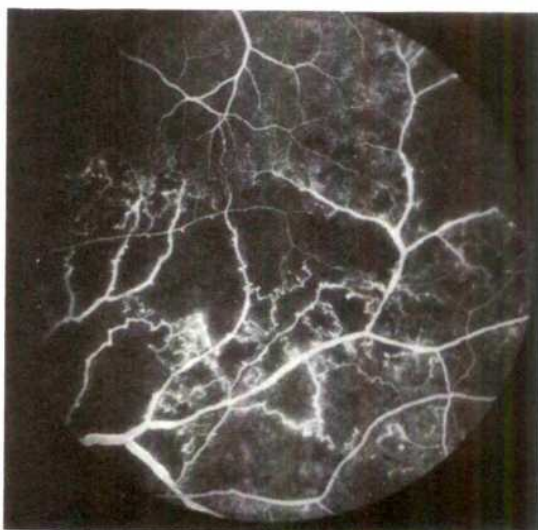


Fig. 6 Fluorescein angiogram of only eye of patient with Behçet's disease. Extensive capillary closure is present with collaterals and marked venous irregularity.

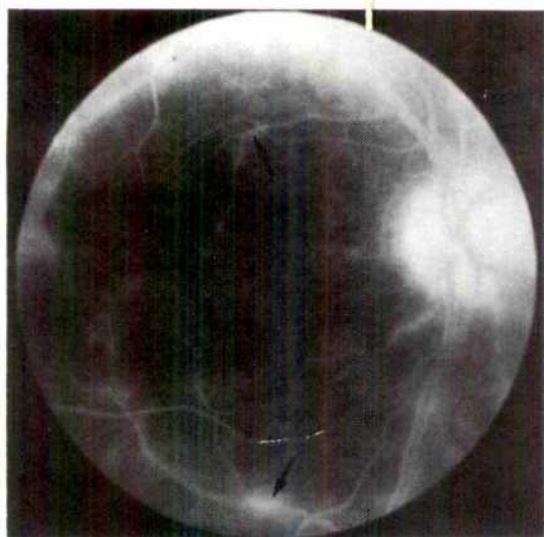


Fig. 7 Late fluorescein angiogram of young man who presented with hemiparesis, facial palsy, and uveitis. Focal leakage of fluorescein from the veins is present (arrows), with some capillary leakage and early macular oedema.

consisted of white lesions in the deep retinal layers, which appeared less fluffy than cotton-wool spots and less dense than retinal exudates ('hard cotton-wool spots') (Fig. 4). Retinal infiltrates were found to be unique to Behçet's disease and did not occur in other systemic inflammatory diseases. Focal atrophic pigment epithelial changes were observed in eight patients with retinal infiltrates and generally evolved as the retinal infiltrates resolved. Anterior uveitis occurred in 19 patients; however, hypopyon was seen in only five, and the other 14 patients had mild anterior uveitis. Fluorescein angiography showed diffuse capillary leakage in all 39 patients (Fig. 5; Table 3), thus emphasising the propensity for involvement of the posterior segment in Behçet's disease. Extensive capillary closure was demonstrated in those patients with recurrent vein occlusions (Fig. 6). The severity of ocular inflammation in this group was reflected by a disease score of more than 10 in 26 patients (67%), a visual acuity of less than 6/18 in one or both eyes in 32 patients (82%) and a reduction of visual acuity to 6/18 in both eyes in 18 of the patients (46%).

SARCOIDOSIS (17 PATIENTS)

The group consisted of seven males and 10 females: 13 were Caucasian, three West Indian, and one Asian Indian; 11 (65%) of the patients were under 40 years of age. The diagnosis of sarcoidosis was confirmed histologically in all cases: seven had positive Kveim tests and in the remainder the diagnosis was con-

firmed by either lung or skin biopsy. Systemic problems included arthritis, erythema nodosum, and neurological disease, but severe pulmonary involvement was not a feature.

The distinguishing ophthalmological feature (Table 2) of this group was retinal periphlebitis associated with focal leakage of fluorescein, which occurred in 11 patients (65%) (Fig 7). Only three patients from this group developed retinal new vessels, and these were in association with capillary closure in two of them. Two-thirds of the patients had disease scores of 10 or less, reflecting only mild or moderate retinal inflammation; only five patients (23%) had significant reduction of visual acuity ($\leq 6/18$) in one eye and only two patients (12%) in both eyes.

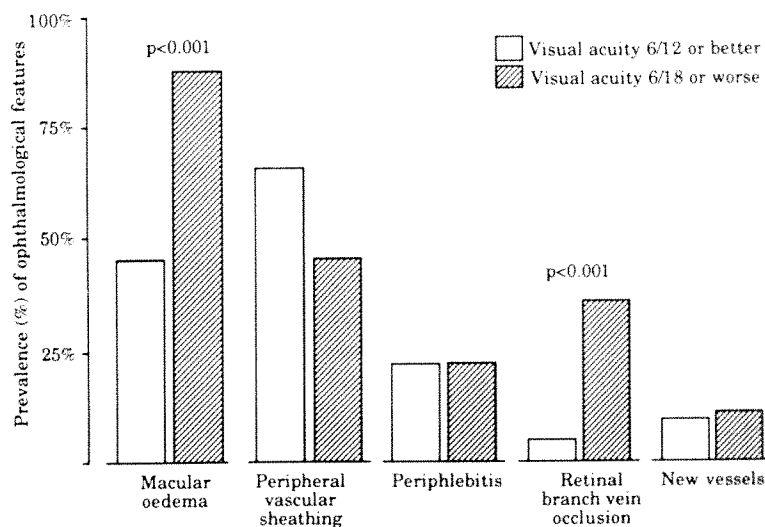
OTHER SYSTEMIC INFLAMMATORY DISEASES (27 PATIENTS)

Eleven patients suffered from retinal vasculitis in association with a significant neurological disorder (uveomeningitis group). In seven patients this was confirmed as multiple sclerosis by a typical history of lesions of the central nervous system disseminated in time and space and by the presence of oligoclonal bands in the cerebrospinal fluid. In the other four the neurological illness could not be attributed to multiple sclerosis or sarcoidosis. The ophthalmological signs (Table 2) did not show any particular features which differentiated this uveomeningitis group from patients with either Behçet's disease or sarcoidosis, though a slightly greater proportion of the patients (45%) developed peripheral sheathing and eight patients (73%) lost vision from macular oedema. The disease score was greater than 10 in six patients (55%) and the visual acuity was less than 6/18 in seven (64%) patients.

Nine patients had retinal vasculitis associated with severe seronegative arthritis, of which five were HLA B27-positive (Table 2). Macular oedema was most prevalent in this group, and two patients lost vision from serous retinal detachment. Similarly, the patient with Crohn's disease also suffered macular oedema and diffuse capillary leakage.

Retinal arteriolar occlusion with consequent capillary closure was seen in the two patients with systemic lupus erythematosus, and the patient with polyarteritis nodosa had a central retinal artery occlusion. The patient with Wegener's granulomatosis has been reported on elsewhere.¹⁰ He had the non-sarcoidal form of the disease and ophthalmoscopic findings similar to those seen in sarcoidosis, with disc oedema, focal periphlebitis, and pigment epithelial lesions. The two patients with isolated glomerulonephritis developed peripheral vascular sheathing and macular oedema, but retinal vascular occlusion was not observed.

Fig. 8 Association between visual acuity and ophthalmological features of 268 eyes affected by retinal vasculitis. The vertical bars represent the prevalence (in %) of macular oedema, peripheral vascular sheathing, periphlebitis, retinal branch vein occlusion, and new vessel formation in this study. Open bars represent visual acuity 6/12 or better, hatched bars visual acuity 6/18 or worse. The figure shows that poor visual function was particularly associated with macular oedema and branch vein retinal occlusion ($p<0.001$).



COMPARISON OF OPHTHALMOLOGICAL FEATURES BETWEEN PATIENT GROUPS

The most striking observation was that retinal infiltrates were found only in patients with Behçet's disease. Moreover, retinal branch vein occlusions were more frequently found ($p<0.001$) in Behçet's disease (51%) than in either sarcoidosis (12%) or isolated RV (9%). However, periphlebitis was the most significant feature in sarcoidosis, where it occurred more often than in either isolated RV ($p<0.001$) or in Behçet's disease ($p<0.02$) (Tables 1 and 2).

Peripheral vascular sheathing was a significantly prominent feature in patients with isolated RV (64%) in comparison with those with Behçet's disease or sarcoidosis ($p<0.001$). Macular oedema was present in 60% of patients with isolated RV and in 54% of patients with RV+SID, where it was more frequent in Behçet's disease than in sarcoidosis ($p<0.02$). Macular oedema in Behçet's disease was particularly associated with poor vision in comparison with those patients with macular oedema due to either isolated RV ($p<0.001$) or sarcoidosis ($p<0.02$). The patients with HLA B27-positive arthritis were the only group (albeit small) to have serious retinal detachments as a complication of their ocular inflammation (Table 2).

Fluorescein angiography revealed that patients with Behçet's disease had a higher prevalence of diffuse capillary leakage and capillary closure than those with sarcoidosis. In terms of capillary leakage, patients with isolated RV more closely resembled those with Behçet's disease than in sarcoidosis, while in terms of capillary closure patients with isolated RV more closely resembled the sarcoid group.

RELATIONSHIP BETWEEN OPHTHALMOLOGICAL FEATURES AND VISUAL OUTCOME

Fig. 8 depicts the associations between the prevalence of five principal ophthalmological features of retinal vasculitis and visual acuity in 268 eyes (four patients each had one eye enucleated, and in 28 patients only one eye was affected) regardless of whether patients had isolated RV or RV accompanying systemic inflammatory disease. One hundred and thirty-one eyes had a visual acuity of 6/12 or better and 137 eyes had a visual acuity of 6/18 or worse. Fig. 8 shows that macular oedema was associated with poor visual acuity ($p<0.001$), and that retinal branch vein occlusion was also a significant factor in visual morbidity ($p<0.001$). However, the prevalence of vascular sheathing (45–65%), periphlebitis (24%), and retinal neovascularisation (12–13%) was not significantly different between eyes with good or bad visual acuity.

Discussion

This study of 150 patients was undertaken to determine whether any ophthalmological features of retinal vasculitis (RV) could distinguish patients with isolated RV from those with RV accompanying systemic inflammatory disorders (Behçet's disease, sarcoidosis, systemic lupus erythematosus); to identify the patterns of eye disease within these groups of patients; and to determine the relation of ophthalmological features to visual acuity. All the patients had cells in the vitreous and involvement of the retinal vessels, which differed in detail within the patient groups. Previous reports have described different patterns of retinal vasculitis accompanying different

systemic inflammatory diseases,¹¹⁻¹⁴ but this study is distinctive in that it directly compares the ophthalmological features between the specified patient groups.

The significant observations that we found were that branch retinal vein occlusion and retinal infiltrates emerged as features strongly associated with Behçet's disease; that periphlebitis was most prevalent in sarcoidosis; and that peripheral vascular sheathing, though common in all groups, was particularly prevalent in isolated retinal vasculitis (Tables 1 and 2). Retinal vasculitis was only rarely associated with severe seronegative spondylarthropathy, but when it occurred it presented as diffuse capillary leakage with macular oedema and serous retinal detachment without retinal vascular occlusion. Both ophthalmoscopy and fluorescein angiography revealed that the capillaries and the postcapillary venules were preferential sites of retinal inflammation in all these patients, whether or not the retinal vasculitis was associated with a systemic inflammatory disease. In contrast, vitreous cells and fluorescein leakage from postcapillary venules were rarely seen in patients with systemic vasculitis or Wegener's granulomatosis. In the systemic vasculitides the inflammatory reaction is known to predominantly affect the arterioles¹⁵; and, although retinal arteriolar occlusion may occur, it is usually due to local thrombus formation rather than to an active inflammation of the retinal vessel wall.¹⁶

The ophthalmological features would seem to reflect the pathological changes going on elsewhere in the body. In Behçet's disease the prominent clinical symptoms are related to the veins (for example, thrombophlebitis, vena caval obstruction), and the same situation seems to prevail in the eye. Characteristically, the vasculitis of Behçet's disease is accompanied by fibrinoid necrosis, exudation of plasma components, and leucocytic infiltrations; and inflammation of the retinal venules is more prominent than that of the retinal arterioles. In this study the patients with Behçet's disease had higher retinal disease scores and worse visual acuities than the patients in the other groups, which is a reflection of the impact of the disease on the retina. It seems likely that the poor visual prognosis in this group is due to the propensity for vein occlusion with consequent retinal ischaemia rather than simply to macular oedema, for macular oedema was a feature of all the groups, but the patients without Behçet's disease usually had better visual function. The severity of the retinal ischaemia in Behçet's disease is reflected in the low incidence of secondary neovascularisation (of 15%), which is similar to that following ischaemic non-inflammatory arteriosclerotic branch vein occlusion.¹⁷

Periphlebitis was a particularly characteristic

feature of retinal vasculitis accompanying sarcoidosis. A clinicopathological study by Gass and Olson¹⁸ has revealed invasion of the retinal vessel wall by inflammatory cells in these areas, often adjacent to non-caseating epithelioid cell granulomata, and it is likely that macrophage activation products are involved in the pathogenesis of chronic inflammation at these sites.

Eleven patients had retinal vasculitis in association with severe neurological disease, which was confirmed as multiple sclerosis in seven patients. All of these seven patients presented with floaters and did not develop neurological problems for a period ranging from six months to nine years after presentation with their ocular disease. In 1944 Rucker¹⁹ described sheathing of the retinal veins in patients with multiple sclerosis, and other authors have since confirmed his findings.²⁰ All Rucker's patients had normal retinal function, with a few vitreous cells and venous sheathing. However, our seven patients showed a variety of changes ranging from similar mild disease to severe retinal involvement with vascular occlusion, capillary closure, neovascularisation, and vitreous haemorrhage. To the ophthalmologist these latter patients are more akin to patients with sarcoidosis. However, pathological studies on patients with multiple sclerosis have shown infiltration of the retinal vessel wall with inflammatory cells, and identical changes have been found in the cerebral venules adjacent to plaques of demyelination in these patients. At sites of chronic inflammation both cerebral and retinal endothelial cells can express class II MHC products,²¹ and it is tempting to assume that a similar immunopathological process underlies both lesions. More detailed study of the retinal vascular changes in such patients with a uveomeningitic syndrome may well improve the understanding of the pathogenesis of multiple sclerosis.

Pathological studies of patients with retinal vasculitis are sparse, and there have not been any 'complete' necropsy reports of such patients. At the present time it is not possible to prove that isolated retinal vasculitis is indeed 'isolated', though all clinical investigation would support this presumption.

Within the limitations of a point-prevalence study examination of these 150 patients has shown that different patterns of retinal vasculitis occur in different systemic inflammatory diseases and that, in isolated retinal vasculitis, peripheral vascular sheathing, macular oedema, and diffuse capillary leakage seem to be associated with one another (Tables 1-3). The features of macular oedema and branch vein occlusion emerged as particularly associated with poor visual function (Fig. 8). In systemic inflammatory disease the patterns of retinal involvement

would seem to reflect the nature of the pathological process in the rest of the body. However, all these systemic diseases are of an idiopathic nature, and further investigation of retinal involvement may yet identify aetiological or precipitating factors for these ill-understood clinical entities.

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A point prevalence study of 150 patients with idiopathic retinal vasculitis: 2. Clinical relevance of antiretinal autoimmunity and circulating immune complexes

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SUMMARY This study describes the occurrence of antiretinal antibodies and circulating immune complexes in the sera of a large series of patients with idiopathic retinal vasculitis whose ophthalmological and clinical features are presented in Part 1. Antiretinal antibodies were measured by indirect immunofluorescence and passive haemagglutination, and circulating immune complexes were measured by polyethylene glycol precipitation and Clq binding. The occurrence of antiretinal antibodies and that of circulating immune complexes were analysed in relation to each other, to severity of retinal disease, to the type of associated systemic inflammatory disease, and to the presence of individual features of retinal inflammation. In patients with retinal vasculitis together with systemic inflammatory disease circulating immune complexes were usually accompanied by antiretinal antibodies. However, those patients with antiretinal antibodies in the absence of circulating immune complexes tended to have more severe retinal vasculitis, a feature particularly evident in Behçet's disease ($p=0.028$). In patients with isolated retinal vasculitis, severity of disease was associated with antiretinal antibody ($p=0.013$), as well as with the occurrence of both antiretinal antibody and circulating immune complexes together ($p=0.010$). In the series as a whole there was a tendency for individual features of retinal vasculitis to be associated with antiretinal antibodies unaccompanied by circulating immune complexes; especially in macular oedema ($p=0.028$). In isolated retinal vasculitis there was also an additive effect of antiretinal antibodies and circulating immune complexes in relation to disease severity; in contrast, in patients with systemic inflammatory disease, the coexistence of antiretinal antibodies and circulating immune complexes was associated with less severe retinal inflammation ($p=0.014$). It is concluded that both antiretinal autoimmunity and circulating immune complexes may act as immunopathogenetic factors in idiopathic retinal vasculitis but that, in certain patients, circulating immune complex formation seems to protect against the more severe forms of autoimmune retinal inflammatory disease.

The eye was the first organ in which inflammation was ascribed to immunopathological mechanisms,¹ yet after eighty years the pathogenesis of much ocular inflammatory disease remains ill understood.² However, there is growing evidence that idiopathic retinal

vasculitis is in fact immunologically mediated; for though this may occur in isolation, the disease is frequently associated with systemic inflammatory disorders in which the immune system is known to be abnormal,² and in either situation retinal inflammation may respond to immunosuppressive therapy.³ Moreover, experimental models of uveoretinitis can

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be produced by autosensitisation with retinal proteins, and previous work has pointed to associations between circulating immune complexes and anti-retinal autoimmunity in the human disease.⁴⁻¹⁰

In the preceding paper we describe in detail the ophthalmological features of 150 patients with idiopathic retinal vasculitis, 83 of whom had concomitant systemic inflammatory disease. In this paper we report on the occurrence of antiretinal antibodies and circulating immune complexes in this large group of patients. The study was undertaken to extend our earlier findings in a smaller group of patients⁴ and to clarify whether these immunological criteria would discriminate patients with isolated retinal vasculitis (RV) from those with retinal vasculitis accompanying systemic inflammatory disease (RV+SID). An additional objective was to determine whether these immunological criteria, singly or together, would reflect the associated systemic disease or the form and severity of retinal inflammation.

Materials and methods

PATIENTS

Of the 150 patients described in the preceding paper⁴ a complete study of antiretinal antibodies (ret-AB) and circulating immune complexes (CIC) was obtainable in 142. Of these, two categories were specified: 63 patients had isolated retinal vasculitis (RV) and the remaining 79 had retinal vasculitis in association with systemic inflammatory disease (RV+SID). The latter category consisted of 38 patients with Behçet's disease (RV+Behçet's) and 14 patients with sarcoidosis (RV+sarcoid); the remaining 27 patients had other inflammatory diseases (RV+other SIDs), which included 11 with neurological abnormalities ('uveomeningitis group') and nine with seronegative polyarthritis, of which five were HLA B27-positive.³

MEASUREMENT OF ANTIRETINAL ANTIBODIES

Two methods were used: passive haemagglutination (Hagg) and indirect immunofluorescence (IIF). In the passive haemagglutination test bovine retinal-S-antigen¹¹ was coupled to sheep erythrocytes with the aid of chromium chloride.⁷ Serial dilutions of patients' sera, in 20 µl volumes, were incubated in microtitre plates with equal volumes of 1% S-antigen coated red cells for two hours at room temperature, and the degree of haemagglutination was scored on a 4-point scale of + to +++++. Antibody titre was expressed as the highest serum dilution giving definite (+) agglutination. In the indirect immunofluorescence test cryostat sections of snap frozen human retina were used as substrate. The tissue specificity of antiretinal immunofluorescence was established by reference to a standard polyclonal guineapig anti-

serum, raised against bovine S-antigen. Retinal-specific immunofluorescence was given by the photoreceptor layers of cones and rods, the cytoplasm of the outer nuclear layer, and the outer plexiform layer. A series of 57 sera from healthy control laboratory staff were examined by passive haemagglutination and by indirect immunofluorescence for the presence of antiretinal antibodies. By haemagglutination 53 of these sera had a titre of $\leq 1:8$, and by immunofluorescence 50 were negative at a dilution of 1:5. Accordingly, the patients' sera were regarded as positive for antiretinal antibodies when these gave either a titre of $\geq 1:32$ by haemagglutination or a titre of $\geq 1:10$ by immunofluorescence.

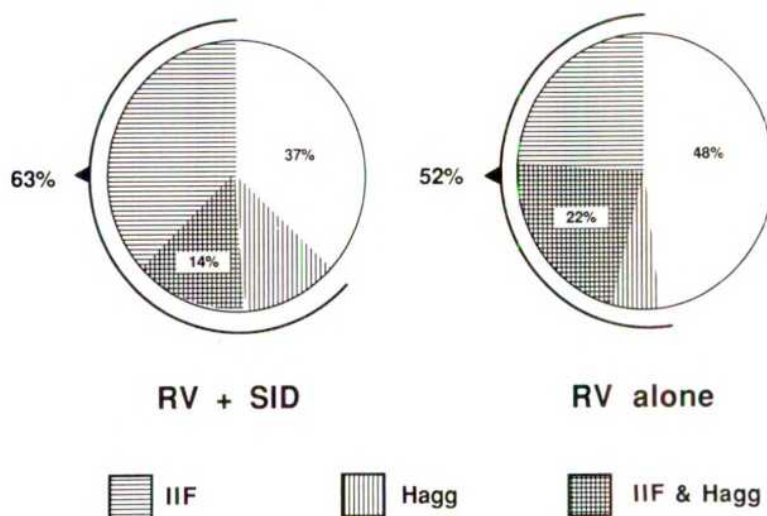
MEASUREMENT OF CIRCULATING IMMUNE COMPLEXES

Two methods were used: a polyethylene glycol (PEG) precipitation test and a Clq solid phase radiometric assay. In the PEG test the serum was precipitated with 2% polyethylene glycol and the IgG content of the precipitate was evaluated by radial immunodiffusion.¹² The Clq binding test was done by a modification of the method of Hay *et al.*¹³ Appropriately diluted sera were incubated in tubes coated with human Clq; immune complex levels were determined by subsequent reactivity with a ¹²⁵I-labelled antiglobulin reagent, and the test was calibrated with aggregated human IgG. Our modification comprised the preincubation of Clq-coated tubes with non-labelled rabbit antihuman IgG (Fcγ), which helped to reduce the background uptake of labelled antiglobulin and to minimise false negative results in sera containing rheumatoid factors. Both PEG and Clq tests were validated in selected patients with renal, rheumatic, and haematological diseases, and in a large panel of healthy subjects. The following ranges of normal values were obtained: Clq-CIC, 20-6 (SD 2.6) mg IgG/l of serum; and PEG-CIC, 25 (SD 12) mg IgG/l of serum. CIC levels were deemed to be raised when the results were more than 2 SD above the normal mean: that is, when either the Clq test gave a value in excess of 25.8 mg IgG/l or the PEG test gave a value exceeding 49 mg IgG/l.

STATISTICAL ANALYSIS OF THE DATA

All clinical and immunological data were entered into a computer. Patients in the two major categories (RV alone, RV+SID), or in the three groups with concomitant systemic disease, or displaying defined ophthalmological criteria, were selected for comparative analysis of immunological and clinical features. Data were analysed by means of the Student's *t* test or by constructing 2×2 contingency tables and calculating χ^2 and *p* values to evaluate the significance of associations between respective features.

Fig. 1 Prevalence of antiretinal antibodies in the two patient categories as detected by indirect immunofluorescence (IIF titre $\geq 1:10$) or passive haemagglutination (Hagg titre $\geq 1:32$).



Results

PREVALENCE OF ANTIRETINAL AUTOIMMUNITY

The sera of 83 patients (58%) were found to have antiretinal antibodies as measured by either passive haemagglutination (titres $\geq 1:32$) or indirect immunofluorescence (titres $\geq 1:10$). Fig. 1 shows that by these criteria (see 'Methods') antiretinal antibodies were more prevalent in the sera of patients with RV+SID (63%) than those with RV alone (52%), but that in the latter category there were more patients whose sera were positive in both tests (22%) than in the RV+SID category (14%). Of the 57 normal sera also examined one gave a haemagglutination titre of $\geq 1:32$ and a second was positive by immunofluorescence at a dilution of 1:10. In this study the prevalence of antiretinal antibodies in

normal sera was accordingly taken as 2/57 (i.e. 3.5%).

PREVALENCE OF RAISED LEVELS OF CIRCULATING IMMUNE COMPLEXES

The sera of 56 patients (39%) were found to have raised levels of CIC as measured by either Clq binding or PEG precipitation. Raised CIC levels were equally distributed between the two patient categories: RV alone, 25/63 (40%); and RV+SID, 31/79 (39%). Table 1 shows that the majority of CIC-positive sera were detected by the Clq binding test: in patients with RV alone these comprised 76% of all CIC-positive sera, while the respective figure for the RV+SID category was 65%. Immune complexes detected by the PEG method were less prevalent in both patient categories (RV alone, 32%; RV+SID,

Table 1 Prevalence of raised levels of circulating immune complexes (CIC) in the sera of two categories of patients with idiopathic retinal vasculitis

Category of patients	CIC positive sera*	Proportion of CIC-positive sera reacting in:		
		Clq binding test	PEG precipitation test	Both Clq and PEG tests together
RV alone	25 (40%)	19/25 (76%)	8/25 (32%)	2/25 (8%)
RV+SID	31 (39%)	20/31 (65%)	14/31 (45%)	3/31 (10%)

*CIC-positive sera were defined as those giving positive values in either the Clq or the PEG test (see 'Methods')

Table 2 Prevalence of antiretinal antibodies and raised levels of circulating immune complexes in different patient groups

Patient group (and no.)	Prevalence of immunological abnormalities		
	Antiretinal antibodies	Raised CIC	Both antiretinal antibodies and raised CIC
RV alone	(63)	33 (52%)	25 (40%)
RV+Behçet's	(38)	21 (55%)	12 (32%)
RV+sarcoid	(14)	10 (71%)	6 (43%)
RV+other	(27)	19 (70%)	13 (48%)
SIDS	(27)	19 (70%)	13 (48%)
All patients	(142)	83 (58%)	56 (39%)

Table 3 Prevalence of antiretinal antibodies in the two patient categories in relation to their circulating immune complex (CIC) status

Patient category	Prevalence of antiretinal antibodies				Significance of difference (p value)
	in CIC-positive sera	%	in CIC-negative sera	%	
All patients	38/56	68	45/86	52	0.066
RV alone	14/25	56	19/38	50	>0.5
RV+SID	24/31	77	26/48	54	0.036

45%). It was of interest that few sera (8-10%) gave positive results in both CIC tests (Table 1).

PREVALENCE OF ANTIRETINAL ANTIBODIES AND CIRCULATING IMMUNE COMPLEXES IN DIFFERENT PATIENT GROUPS

Table 2 displays the prevalence of and association between antiretinal antibodies and raised levels of CIC in patients with RV alone and in the three groups of the RV+SID category: RV+Behçet's disease, RV+sarcoid, and RV+other SIDs. There was a similar proportion of patients with antiretinal antibodies in the RV alone (52%) and RV+Behçet's disease (55%) groups, while the rest of the patients with systemic inflammatory disease had a higher incidence of antiretinal antibodies (70-71%). Raised levels of CIC were found in the sera of 39% of all patients and in 40% of those with RV alone. There were, however, some variations in the prevalence of

CIC within the RV+SID category of patients. Thus, raised CIC were found in 32% of sera of patients with RV+Behçet's disease, in 43% of the RV+sarcoid group, and 48% of the group with RV+other SIDs.

Table 3 and Fig. 2 show associations between antiretinal antibodies and raised levels of CIC in the total patient population, in the two major patient categories, and in the individual groups of the RV+SID category. When all patients were considered, 68% of those with raised levels of CIC also had antiretinal antibodies, while only 52% of the patients with normal CIC levels were antibody-positive ($p=0.066$). In the RV+SID category 77% of CIC-positive patients had antiretinal antibodies, while only 54% of CIC negative patients did so ($p=0.036$). In contrast, in patients with RV alone antiretinal antibodies were equally prevalent in patients with raised (56%) and normal (50%) levels of CIC (Table 3). In all patient groups the proportion of positive sera reactive only for antiretinal antibodies was greater than the proportion of positive sera reactive only for circulating immune complexes (Fig. 2). Thus in RV alone, of the 33 antibody-positive patients 19 (58%) were CIC-negative, while of the 25 CIC-positive patients 11 (44%) were antibody-negative; and this pattern was reflected in the other patient groups (Fig. 2). However, the proportion of sera within each patient group that contained both antiretinal antibodies and CIC together was similar (22-29%) with the exception of the RV group associated with SIDs other than sarcoid or Behçet's disease, where it was somewhat higher (41%: Table 2).

Percentage positive sera reactive for AB or CIC only

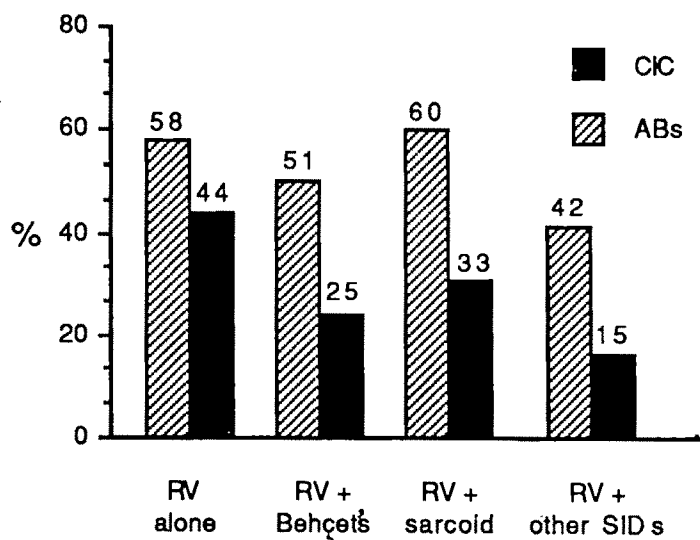


Fig. 2 Respective proportions of antibody-positive and CIC-positive sera in the different patient groups that expressed antiretinal antibodies only (hatched bars) or circulating immune complexes only (solid bars).

Table 4 Prevalence of antiretinal antibodies in relation to CIC status and disease score in the two patient categories

Patient category	Retinal disease score	Prevalence of antiretinal antibodies		
		in all sera	in CIC positive sera	in CIC negative sera
RV alone	low (≤ 10)	11/30 (37%)*	3/11 (27%)†	8/19 (42%)
	high (> 10)	22/33 (67%)*	11/14 (79%)†	11/19 (58%)
RV+SID	low (≤ 10)	28/42 (67%)	15/19 (79%)	13/23 (56%)
	high (> 10)	22/37 (59%)	9/12 (75%)	13/25 (52%)

* $p=0.013$. † $p=0.010$.

ASSOCIATION BETWEEN DISEASE SEVERITY AND IMMUNOLOGICAL STATUS

The severity of retinal inflammation was graded by means of a points system in which ophthalmological features were assigned a value according to their considered impact on visual morbidity.⁶ The total number of points for both eyes of each patient was recorded, and retinal disease severity was classified, firstly, as either 'low score' (1-10 points) or 'high score' (> 10 points). The prevalence of CIC and retinal antibodies, either separately or in association with each other, was compared in patients with high and low disease scores, in the two categories RV alone and RV+SID. Table 4 shows that, in RV alone, there was a higher prevalence of antiretinal antibodies in patients with higher (67%) rather than lower (37%) disease scores ($p=0.013$). This was particularly evident in patients who also had raised CIC levels ($p=0.010$). In contrast, in the RV+SID

patient category there was no overall association between disease severity and the prevalence of antiretinal antibodies: the prevalence of antiretinal antibodies was slightly lower (59%) in patients with a high disease score than in those with a low disease score (67%). Moreover, RV+SID patients with raised CIC levels tended to have antiretinal antibodies, whether they had high or low disease scores (Table 4).

The question arose whether antiretinal antibodies and CIC might act together in the pathogenesis of retinal vasculitis. Fig. 3 shows the proportion of patients with a high disease score showing antiretinal antibodies only, circulating immune complexes only, or the two immunological abnormalities together. In RV alone the majority of patients displaying both immunological abnormalities belonged to the high-score category (11/14; 79%), while in RV+SID a relative minority (9/24; 38%) of such patients had high-score disease ($\chi^2=5.98$; $p=0.014$). Fig. 3 also demonstrates that the prevalence of patients with a high disease score in the RV alone category, who had both CIC and antiretinal antibodies together, bore an additive relationship to those with either CIC or antiretinal antibodies alone. In contrast, the prevalence of patients with a high disease score in the RV+SID category who had both immunological abnormalities together was actually lower than in those who had either CIC or antiretinal antibodies alone.

Patients in both categories were then analysed by criteria of disease group, mean disease score (DS), and 'severe' retinal disease (> 20 points). Of the 78

Fig. 3 Respective proportions of patients with high disease scores (> 10 points) in RV alone (solid bars) and RV+SID (hatched bars) whose sera contained either circulating immune complexes (CIC) only, antiretinal antibodies (ABs) only, or CIC and ABs together.

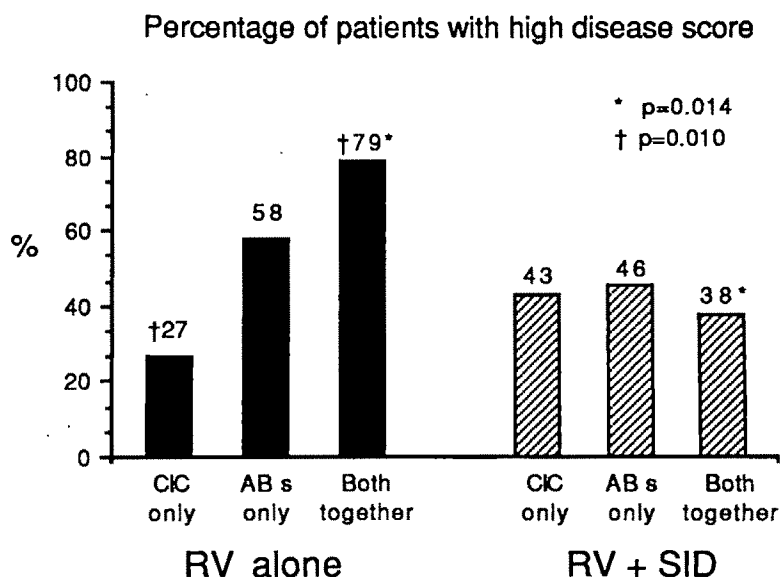


Table 5 Relationship between disease severity, antiretinal antibodies, and presence of circulating immune complexes in retinal vasculitis accompanying Behçet's, Sarcoidosis, and other systemic inflammatory disease

Patient group and disease score (DS)	Antiretinal antibodies present			Antiretinal antibodies absent
	Totals	CIC positive	CIC negative	
<i>RV+Behçet's:</i>	21	9	12	17
DS>20 points	8/21	1/9*	7/12*	5/17
Mean DS (SEM)	16.1(2.1)	11.9(2.7)	17.9(2.9)	17.1(2.3)
<i>RV+sarcoid:</i>	10	4	6	4
DS>20 points	1/10	0/4	1/6	0/4
Mean DS (SEM)	12.2(4.0)	8.5(1.9)	14.7(7.3)	9.2(2.5)
<i>RV+other SID:</i>	19	11	8	8
DS>20 points	3/19	2/11	1/8	0/8
Mean DS (SEM)	9.8(2.0)	9.1(2.9)	11.3(3.4)	6.3(1.7)

*Behçet's+severe RV, antibody positive:

CIC-positive, 1/9
CIC-negative, 7/12 } $p=0.028$

Non-Behçet's+severe RV:

AB-positive, 4/29
AB-negative, 0/12 } $p=0.18$

Mean disease scores of AB-positive patients:

CIC-positive (n=26), 10.0 (SEM 1.7)
CIC-negative (n=25), 14.9 (SEM 2.3) } $p=0.1$

RV+SID patients 17 (22%) had severe retinal disease. Table 5 shows that seven of the eight patients with Behçet's disease and severe RV had antiretinal antibodies in the absence of circulating immune complexes ($p=0.028$); that in patients without Behçet's disease (41) the few patients with severe retinal disease (DS>20 points) were all antibody-positive (4/29), while none of 12 antibody-negative patients had severe retinal disease. In the RV+SID category as a whole there was a tendency for antibody-positive patients without raised CIC to have higher retinal disease scores than those with

raised CIC levels ($p=0.1$, Table 5). Thus in the RV+SID category there was evidence that certain patients with antiretinal autoimmunity and absent circulating immune complexes had severe retinal disease.

Of the 63 patients with RV alone only eight (13%) had severe retinal disease (DS>20 points), though the mean disease score of the 63 patients (11.6 (SEM 4.0)) was similar to that of the 78 patients with RV+SID (mean: 11.5 (SEM 3.8)). In the 33 patients with RV alone who were antibody-positive (Table 2) there was no significant difference between the mean disease score of the 14 who were CIC-positive (14.5

Table 6 Association between principal features of retinal vasculitis and the prevalence of immunological abnormalities

Features of retinal vasculitis (patient numbers)	Prevalence of circulating immune complexes		Prevalence of antiretinal antibodies	
	Total	Proportion with antiretinal antibodies	Total	Proportion with circulating immune complexes
<i>Macular oedema</i>				
Present (80)	25/80*	18/25	50/80	18/50†
Absent (62)	31/62*	20/31	33/62	20/33†
<i>Periphlebitis or perivascular sheathing</i>				
Present (98)	39/98	25/39	59/98	25/59
Absent (44)	17/44	13/17	24/44	13/24
<i>Capillary closure or capillary leakage</i>				
Present (87)	30/87	19/30	49/87	19/49‡
Absent (55)	26/55	19/26	34/55	19/34‡
<i>Vein occlusions or new vessels</i>				
Present (40)	11/40	8/11	23/40	8/23
Absent (102)	45/102	30/45	60/102	30/60

* $p=0.023$. † $p=0.028$. ‡ $p=0.13$.

points) and the 19 who were CIC-negative (12.4 points). Unlike the RV+SID category (see above), there was no subgroup of patients with RV alone that had an apparent 'syndrome' of antiretinal autoimmunity, absent circulating immune complexes, and severe retinal disease.

ASSOCIATION OF IMMUNOLOGICAL ABNORMALITIES WITH FEATURES OF RETINAL VASCULITIS

Table 6 displays the prevalence of circulating immune complexes and antiretinal antibodies in relation to four principal features of retinal vasculitis in the whole series of patients, and it shows that there was a tendency for the individual features to be associated with antiretinal antibodies unaccompanied by circulating immune complexes.

Macular oedema. More than half (56%) of all the patients in the study had evidence of macular oedema. Antiretinal antibodies were found more frequently in patients with macular oedema (63%) than in those who had a normal macula (53%), though the difference was not statistically significant. However, as shown in Table 6, there was a significantly lower incidence of raised CIC in patients with macular oedema in comparison with those with normal macula ($p=0.023$); and antiretinal antibodies were less frequently accompanied by CIC in these patients ($p=0.028$; see Table 6).

Periphelebitis and perivascular sheathing. Ninety-eight patients (69%) had one or both of these two clinical features. Of these patients 59% had antiretinal antibodies and 39% had raised CIC levels. The prevalence of these immunological features was the same as in the total population of 142 patients studied (see Table 2). There was a tendency for a higher frequency of CIC unaccompanied by retinal antibodies in the sera of patients with perivascular sheathing or periphelebitis (35%) in comparison with those without (22%).

Capillary closure and/or leakage. Eighty-seven patients (61%) had evidence of capillary closure or leakage as judged by fluorescein angiography. The prevalence of antiretinal antibodies (58%) and CIC (23%) in patients with these clinical features was not dissimilar to that in the total population of patients studied. There was a tendency for patients with capillary closure or leakage to have a higher frequency of antiretinal antibodies in the absence of CIC (61%) in their sera in comparison with those who did not have these retinal features (44%), where antiretinal antibodies tended to be more associated with CIC.

Vein occlusion or new vessels. These two clinical features were found in 40 patients only. The prevalence of antiretinal antibodies in the sera of these patients (59%) was the same as in the whole popula-

tion studied, but raised CIC levels tended to occur less frequently (28%) in patients with vein occlusion or new vessels than in patients without these features (45%; $p=0.068$). The majority (65%) of antiretinal antibodies in the sera of patients with vein occlusion or new vessels were unaccompanied by raised levels of CIC, while antiretinal antibodies in patients without these features were equally distributed between CIC-positive and CIC-negative sera.

Discussion

In this paper we report on the prevalence of antiretinal antibodies and circulating immune complexes in 63 patients with isolated retinal vasculitis and 79 patients with retinal vasculitis accompanying systemic inflammatory diseases—data obtainable on 142 of the 150 patients whose clinical and ophthalmological features are described in the preceding paper.³ In extending our earlier work⁶ we undertook this much larger study to determine whether patients with isolated retinal vasculitis (RV alone) would have a different immunological profile from those with retinal vasculitis accompanying systemic inflammatory disease (RV+SID) and to determine whether these immunological features would reflect the nature of associated systemic disease or the form and severity of retinal inflammation.

There have been a few reports concerning the presence of antiretinal antibodies in uveitis syndromes and these have stimulated some controversy.⁷⁻¹⁰ Thus in 1981 Gregerson's group⁸ reported a 60% prevalence of antibody to retinal S-antigen in a series of patients with a wide spectrum of uveitis; this finding was recently challenged by Doekes *et al*⁹ who used a similar immunochemical technique (ELISA) but could not discriminate between uveitis patients and normal controls, both of whom had the same prevalence (28-30%) of antibody to S-antigen. This study confirms our previous finding that both by immunofluorescence and passive haemagglutination antiretinal antibodies can be detected readily in patients with idiopathic retinal vasculitis⁶ and reports that their prevalence in retinal vasculitis (58%) far exceeds that in normal individuals (3.5%).

It is likely that the prevalence of immunological abnormalities in uveitis syndromes depends both on the technique of detection and the clinical criteria on which the patient population is defined. Our previous finding of circulating immune complexes (CIC) in retinal vasculitis⁶ was in accord with the findings of Char *et al*¹¹ on uveitis sera, and the prevalence of CIC in the present study (40%) provides further confirmation of this. We have accordingly proceeded to identify associations between the prevalence of antiretinal antibodies and circulating immune complexes

in this larger series of patients with well characterised retinal vasculitis,³ with particular reference to the clinical interpretation of these immunological abnormalities.

In the present study a majority of the circulating immune complexes (CIC) were complement (Clq)-binding and very few sera were positive by both the Clq and PEG tests (Table 1). In all groups of patients the proportion of sera reactive only for antiretinal antibodies was greater than the proportion of sera reactive only for CIC (Fig. 2), suggesting the greater relevance of autoimmune rather than immune-complex mediated pathogenetic mechanisms. However, antiretinal antibodies tended to be more prevalent in CIC-positive sera ($p=0.066$, Table 3); and, while this association was dominated by the RV+SID category ($p=0.036$, Table 3), it was a particular feature of patients with systemic diseases other than Behçet's disease and sarcoid (Table 2). In terms of the mere prevalence of these immunological abnormalities patients with retinal vasculitis accompanying Behçet's disease appeared to resemble those with isolated retinal vasculitis more closely than those with other systemic inflammatory diseases (Table 2). Further immunochemical investigation—of the size and composition of the immune complexes and of the isotype and complement-fixing ability of the antiretinal antibodies—would clarify whether the qualitative nature of these immunological reactants could be of additional clinical significance.

When retinal disease score was also considered, the two major patient categories showed different patterns of association between the prevalence of antiretinal antibodies, CIC, and severity of retinal disease. Patients with RV alone, of disease score greater than 10 points, had a significantly higher prevalence of antiretinal antibodies than those with a lower disease score, while there was no such difference in the RV+SID category as a whole (Table 4). The findings that, in RV alone, antiretinal antibodies were preferentially associated with CIC positivity in patients with the higher disease scores (Table 4) suggests that both antiretinal autoimmunity and circulating immune complex formation contribute to the pathogenesis of isolated retinal vasculitis. In terms of disease severity there appeared to be an additive effect of antiretinal antibodies and CIC together in RV alone, where patients with both immunological abnormalities had significantly more severe retinal disease than those with CIC only ($p=0.010$, Fig. 3). In contrast, the combination of both features in patients with RV+SID had no additive effect ($p=0.014$, Fig. 3).

Further analysis revealed that in RV+SID, patients who were positive for both antiretinal antibodies and CIC tended to have the lower mean

retinal disease scores (Table 5); and that in all three groups (RV+Behçet's disease, RV+sarcoid, RV+other SIDs) those with antiretinal antibodies had higher mean disease scores if they were CIC-negative. This was particularly true of the Behçet's disease group, where those who were antibody-positive, CIC-negative, had the highest prevalence of severe retinal vasculitis, with disease scores greater than 20 points ($p=0.028$, Table 5). These findings reinforce our earlier proposition that, in certain patients with retinal vasculitis, CIC formation may indicate the operation of a protective (? anti-idiotypic) host response to antiretinal autoimmunity,⁶ while in other patients CIC formation may add to the pathogenetic impact of autoimmunity on the retina.

The clinical relevance of studying antiretinal autoimmunity and circulating immune complexes in patients with retinal vasculitis would therefore appear to depend on the form of associated systemic disease and on the nature and occurrence of those features of retinal inflammation which contribute to disease severity in the individual patient. In isolated retinal vasculitis it seems that antiretinal antibodies are associated particularly with macular oedema and that the concomitant presence of circulating immune complexes and antiretinal antibodies is associated with more severe disease characterised in addition by perivascular sheathing and diffuse capillary leakage. In retinal vasculitis accompanying systemic inflammatory disease the most severely affected patients are antibody-positive despite anti-inflammatory and immunosuppressive drug treatment. In Behçet's disease antiretinal antibodies may be absent; but, if they are present, the severely affected patient tends to be CIC-negative. Study of a larger group of RV patients with Behçet's disease would be required to determine whether retinal infiltrates, branch vein retinal occlusion and neovascularisation, macular oedema, and diffuse capillary leakage in this condition are specifically associated with one or other immunological profile. In RV accompanying sarcoidosis the most severely affected patients also have antiretinal antibodies unaccompanied by CIC. This finding suggests that periphlebitis and focal vascular leakage in retinal sarcoidosis have an autoimmune rather than an immune-complex pathogenesis. RV patients with other systemic inflammatory diseases, including the uveomeningitic syndrome, tended to have lower disease scores than patients with Behçet's disease or sarcoidosis; however, the most severely affected patients in this additional group were also those who had antiretinal antibodies in the absence of circulating immune complexes.

We conclude that the ophthalmological significance of studying antiretinal autoimmunity and non-tissue-

specific immunological abnormalities in retinal vasculitis may prove to be of diagnostic, prognostic, and pathogenetic value. In diagnostic and prognostic terms the identification of antiretinal autoimmunity may single out those patients at risk of more severe retinal disease or its more frequent relapse.¹⁴ In pathogenetic terms it appears that antiretinal autoimmunity is important in both isolated retinal vasculitis and retinal vasculitis accompanying certain systemic inflammatory diseases. However, the presence of raised levels of circulating immune complexes appears to confer an additional pathogenetic component in isolated RV while appearing to modulate retinal disease severity in the systemic syndromes. The central problem underlying this field concerns an understanding of how antiretinal autoimmunity is regulated and how its pathogenetic impact on the retina is brought about. Our continued study of defined groups of patients with autoimmune retinal vasculitis is aimed at clarifying this intriguing question.

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Orbital malignant peripheral nerve sheath tumours

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SUMMARY We describe three patients with malignant peripheral nerve tumours in the orbit and review the existing literature on these rare lesions.

Malignant peripheral nerve sheath tumours are unusual in any part of the body and very rare in the orbit, where only 13 cases have previously been described. These tumours can spread rapidly along the involved nerve to the middle cranial fossa. They are radioresistant, and total surgical excision offers the only hope of cure. Our experience with three patients may help clinicians to recognise these lesions and excise them at an early stage.

Case reports

PATIENT 1

Four years prior to presentation a 55-year-old man noted a small lump at the medial end of his right lower eyelid. This was removed through the palpebral conjunctiva but recurred within a month. A histopathological report was not obtained.

Over the next two years three further attempts were made to remove this lump surgically with either incomplete removal or early recurrence on each occasion. After three years the lump had extended into the floor of the orbit, and a further attempt at excision was made, by a transantral approach.

Histopathological examination on these occasions showed the features of 'a neurofibroma with schwannian transformation in certain areas'. There was no evidence of malignancy. Despite tumour-free resection margins the mass recurred in the floor of the orbit.

At presentation the right vision was reduced to perception of hand movements. The globe was proptosed 5 mm and displaced inferiorly 6 mm and laterally 9 mm. There was a marked right relative afferent pupillary defect with disc swelling, and movement of the eye was severely restricted.

Sensation was diminished over the distribution of the second division of the right trigeminal nerve. The left globe was normal. Plain anteroposterior skull x-rays showed a normal appearance, but undertilted occipitontal tomographic views revealed enlargement of the right infraorbital canal (Fig. 1).

An inferior orbital margin incision revealed tumour protruding from the infraorbital foramen and extending beneath the soft tissues of the cheek. The tumour had a firm consistency and a pale grey cut surface. The orbital periosteum on the floor of the orbit was elevated and a mass over 18 mm in diameter was found within an expanded infraorbital canal which extended posteriorly into the superior orbital fissure. Biopsy specimens were taken.

Histology

The tumour was composed of a homogeneous and densely packed proliferation of spindle shaped cells aligned in more or less parallel bundles and sheets. In places there was a fascicular pattern with palisading of nuclei, characteristic of Antoni A morphology of a schwannoma (Fig. 2a, b). Looser myxoid areas of Antoni B differentiation were not seen. However, small clear spaces or vacuoles were common, and in some instances the tumour cells were grouped round such spaces to create a pseudoglandular appearance. The reaction for S-100 protein was strongly positive, virtually all the cells being stained (Fig. 2c). The tumour cells had prominent and sometimes multiple nucleoli, were frequently hyperchromatic, and mitotic figures could occasionally be recognised. Scattered giant nuclei were also present. There was no clearly defined capsule, and tumour cells appeared to be infiltrating the adjacent orbital connective tissue. Some haemosiderin resulting from previous haemorrhage was also seen.

Transmission electron microscopy of formalin

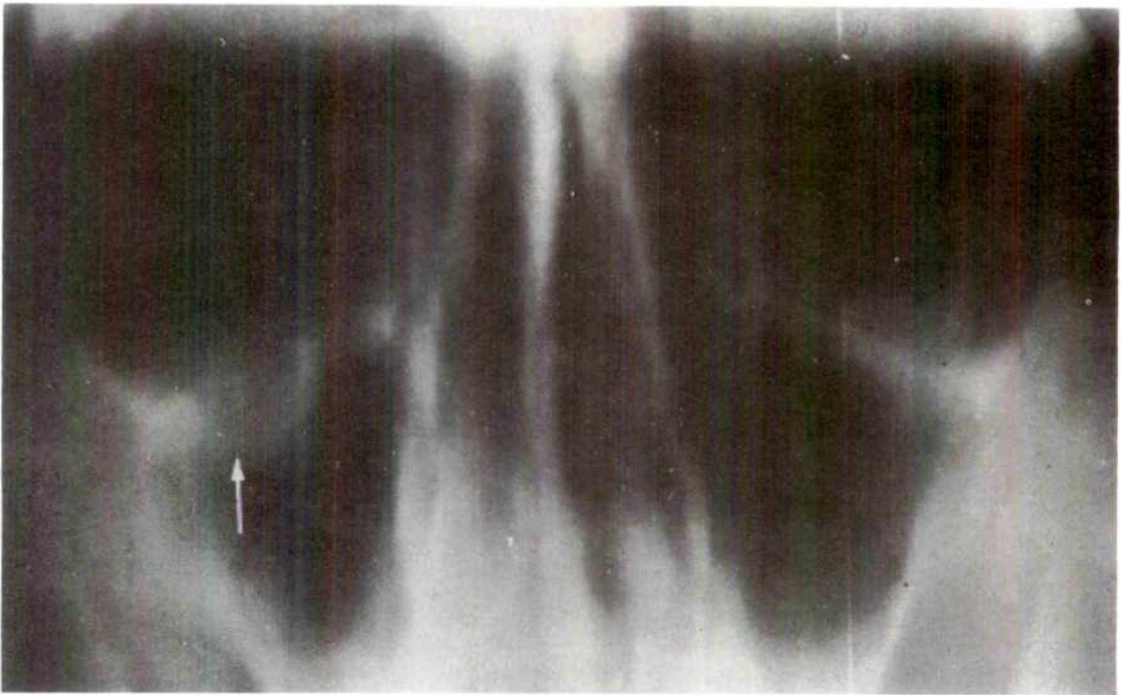


Fig. 1 Patient 1. An undertilted occipitomeatal tomogram shows enlargement of the infraorbital canal caused by tumour (arrow).

fixed tissue revealed cells with grooved or indented nuclei and conspicuous nucleoli. Individual cells were sometimes linked by complexes resembling desmosomes, and there was incomplete basal lamina formation surrounding the cytoplasmic membranes of occasional cells (Fig. 3). Although rare collagen fibres presented exceptionally prominent cross-striations, long-spacing fibres were not identified. A prominent rough-surfaced endoplasmic reticulum was observed in a minority of cells.

The patient was referred for neuroradiological and neurosurgical opinion to determine if the tumour was resectable. The presence of a large mass in the posterior fossa, continuous with the mass in the orbital floor, was confirmed.

By this time, the patient had developed severe paroxysms of lancinating electric shock-like pain involving the whole of the right side of his face and numbness affecting the left side of his body. He had also noticed voice changes and difficulty in swallowing, and he complained of poor balance and difficulty in walking, with a tendency to fall to the right. Palliative radiotherapy was given. The patient died within four months.

PATIENT 2

A 42-year-old man had noticed discomfort round the

left eye and dilated conjunctival blood vessels for eight months. Two months after the onset of these symptoms he had noticed that the left globe was protuberant, and a week before presentation his vision had deteriorated.

At his first attendance his right visual acuity was 6/5 while the left corrected acuity was 6/24. There was a left relative afferent pupillary defect, and the left globe was proptosed 8 mm axially. Ocular movements were restricted in all directions, especially elevation. Facial and corneal sensation was normal.

The left conjunctiva and episclera were markedly hypervascular, but there was no pulsation nor any audible bruit. The disc was swollen.

A CT scan (Fig. 4) showed a large, well defined, rounded and homogeneous mass situated superiorly within the intraconal space. This enhanced with contrast. An intra-arterial digital subtraction angiogram showed a brisk tumour circulation with early filling by contrast (Fig. 5). The provisional diagnosis was haemangiopericytoma.

At lateral orbitotomy a large firm tumour lying intraconally was dissected free of adjacent structures and found to extend to the superior orbital fissure, where it was transected and its stump subjected to diathermy. Postoperatively the visual acuity remained unchanged. One year after the operation,

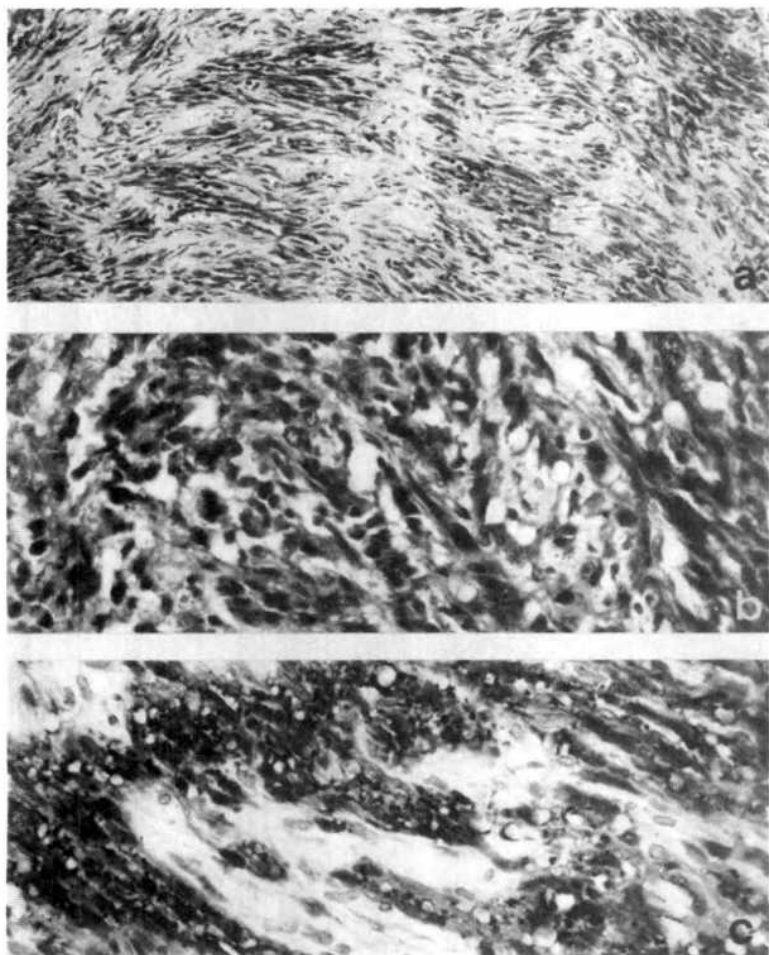


Fig. 2 Patient 1. (a) Cells with elongated, wavy nuclei showing a tendency to a palisade alignment; the histology of the tumour recalls the Antoni A structure typical of schwannoma. (Haematoxylin and eosin, $\times 125$.) (b) In places the tumour cells have abnormally large, hyperchromatic and pleomorphic nuclei and are suggestive of malignancy. (Haematoxylin and eosin, $\times 313$.) (c) There is a conspicuous staining reaction for S-100 protein. (Immunoperoxidase, $\times 125$.)

there was no evidence of local recurrence or distant metastasis.

Histology

Examination of the tumour revealed a highly cellular neoplasm with a predominance of spindle cell forms. In many areas the cells were grouped in fascicles with a rudimentary attempt at a palisade arrangement (Fig. 6a). Other cells were vacuolated, and there was widespread focal lymphocytic infiltration. Lymphoid tissue was also prominent in the compressed connective tissue which partly encompassed the tumour. Some cells had unusually large, pleomorphic, and hyperchromatic nuclei, and many had conspicuous nucleoli, while occasional mitotic figures were also seen (Fig. 6b). Staining for S-100 protein was observed in scattered tumour cells (Fig. 6c). A few myelinated nerve bundles were present in the tissue surrounding the tumour.

Electron microscopy of a separate piece of the tumour failed to provide any evidence of basal lamina formation round the cells or of long-spacing collagen, though the cytoplasmic processes of the cells showed considerable interdigitation.

PATIENT 3

A 21-year-old man had noticed a progressively enlarging painless lump in the medial part of his left upper eyelid for five years. Two previous attempts at surgical excision had failed. The visual acuity was 6/6 in each eye. The left globe was proptosed by 6 mm and displaced laterally by 8 mm. A large mass of soft, almost fluctuant consistency occupied both inner quadrants of the left orbit. There were two surgical scars overlying the mass in the upper lid. CT scans (Fig. 7) revealed an extensive soft tissue mass extending from the skin anteriorly to the posterior limit of the orbit. The orbit was enlarged, and the

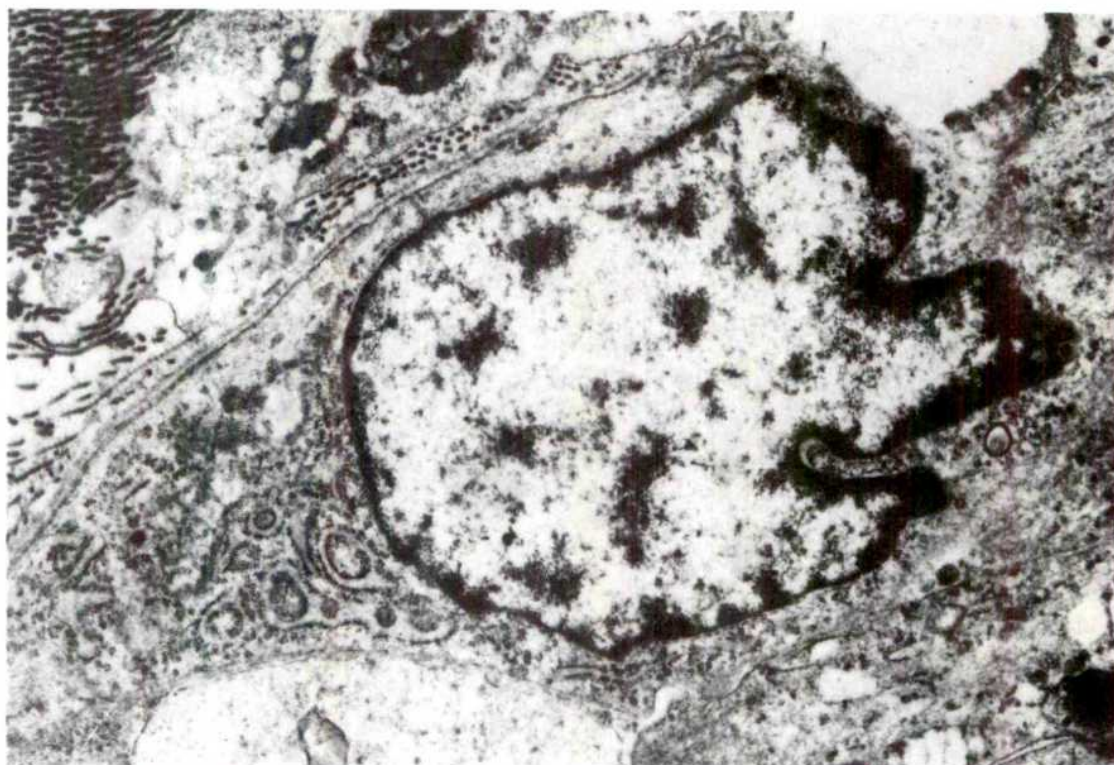


Fig. 3 Patient 1. Transmission electron micrograph showing part of a cell with an indented nucleus and prominent rough endoplasmic reticulum. There is a distinct basal lamina next to the cell surface. (Uranyl acetate/lead citrate, $\times 13\,300$).

mass displaced the medial rectus, optic nerve, and globe laterally. The medial wall of the orbit was intact.

At anterior orbitotomy a large tumour was adherent to the orbital septum and trochlea, and the optic nerve posteriorly. Most of the tumour was removed, but a small part remained in the posterior orbit attached to the optic nerve.

Postoperatively the patient retained 6/6 vision but had limited extraocular movements. Histopathological examination showed the tumour to be a malignant peripheral nerve sheath tumour. Exenteration was advised, but the patient refused and was lost to follow-up.

Histology

The tumour was composed of spindle shaped cells with round, oval, or elongated wavy nuclei and fibrillary cytoplasmic processes (Fig. 8a). The overall structure of much of the tumour was loose, with accumulation of mucoid material and prominent vascularity, but collagen formation was sparse. In some areas there was increased cellularity, a proportion of the cells being pleomorphic with enlarged,

hyperchromatic and, exceptionally, multiple nuclei and readily observed nucleoli (Fig. 8b). A positive staining response for S-100 protein was obtained in respect of only a very few cells (Fig. 8c), though the technique served to demonstrate occasional small myelinated nerve bundles within the substance of the tumour. Scattered mast cells were detected. There was some evidence of a capsule in places, but for the most part the tumour had ill-defined margins and appeared to be infiltrating the orbital connective tissue.

Discussion

HISTOPATHOLOGY

The criteria for recognising malignant peripheral nerve sheath tumours are not fully determined, though the advent of electron microscopical and immunohistochemical techniques has put the diagnosis on rather more certain ground. Consequently reports of such lesions prior to the introduction of these supplementary methods of examination need to be treated with some caution. Four cases diagnosed on conventional histological grounds alone are

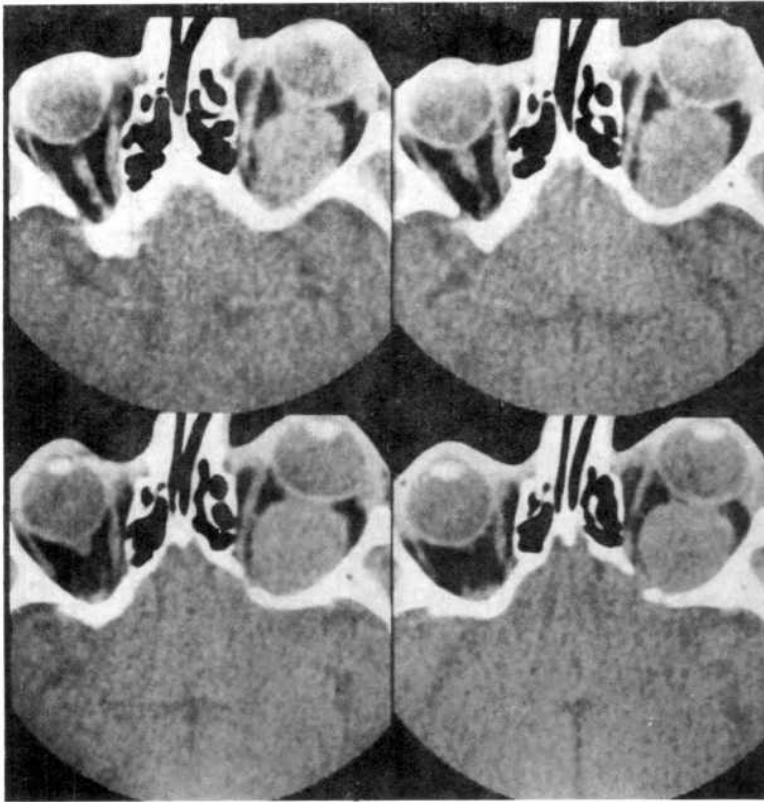


Fig. 4 Patient 2. Axial CT scans with contrast medium show a large well defined and homogeneous intraconal mass extending to the orbital apex.

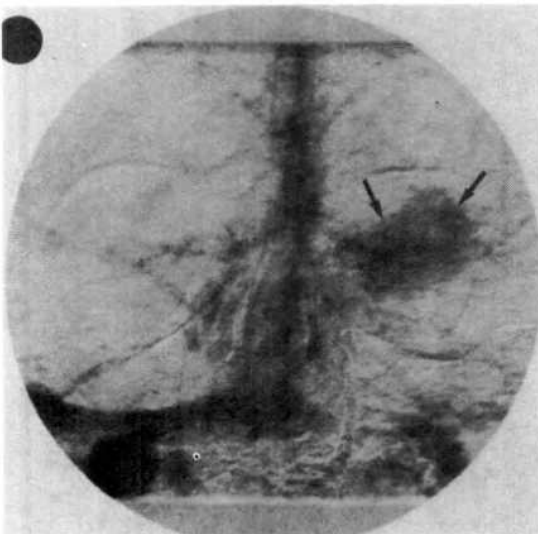


Fig. 5 Patient 2. A digital subtraction angiogram shows a distinct tumour blush within the left orbit (arrows). The tumour filled with contrast early in the arterial phase.

probably acceptable,¹⁻³ and another case was included in a review by Henderson in 1980,⁴ but the best documented series from a pathological point of view are the eight cases reported by Jakobiec *et al.* in 1985.⁵

All the reported cases including ours have been adults, with an age range of 19 to 76 years.

Because it is possible that some malignant tumours arise from the perineural cell or endoneurial fibroblast components of peripheral nerves rather than Schwann cells, there is reason to avoid a terminology which specifies the cell of origin unless this is certainly known. Hence the broader designation of malignant peripheral nerve sheath tumour is preferable to denote the type of neoplasm we have described.

There would seem to be adequate evidence to regard at least two of the present cases as having a primarily schwannian histogenesis. Cases 1 and 2 had an easily identified Antoni A palisade arrangement and gave positive responses for S-100 protein. While the latter is not peculiar to Schwann cells or, possibly, even cells of neural crest origin, its presence in the

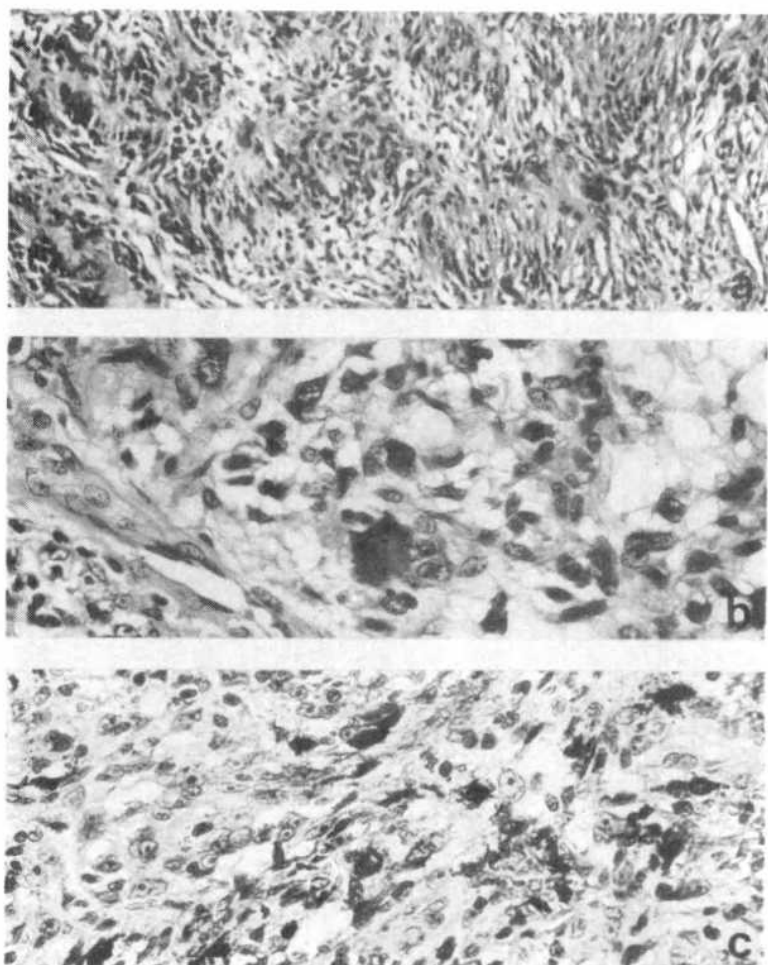


Fig. 6 Patient 2. (a) Part of the tumour showing fascicles of spindle cells arranged in a roughly palisade manner. (Haematoxylin and eosin, $\times 125$). (b) Other parts of the tumour are composed of generally pleomorphic cells with vacuolated cytoplasm and occasionally giant nuclei. (Haematoxylin and eosin, $\times 313$). (c) Scattered cells give a positive reaction for S-100 protein. (Immunoperoxidase, $\times 125$).

context of spindle cell orbital tumours strongly supports the diagnosis of schwannoma.^{6,7} Neither fibroblasts nor smooth-muscle cells stain for S-100 protein. The demonstration of a basal lamina surrounding some cells in the first case is also typical of a schwannoma.^{8,9} Additional features of tumours of schwannian type include pseudomesaxon formation and bundles of long-spacing collagen, but neither was observed in the cases under review. The precise identification of case 3 is less certain, though the finding of cells with elongated wavy nuclei and a frequently myxoid background equivalent to the Antoni B structure associated with schwannomas is in agreement with a peripheral nerve sheath tumour.

The diagnosis of malignancy was based on the presence of cells showing irregularity of size and shape, nuclear enlargement, and hyperchromatism. Mitoses, though seen in each of the three cases, are not a reliable guide to malignancy, and, as others

have commented,⁸ care must be taken not to mistake the hypercellular variant of a benign schwannoma in which there is an almost exclusively Antoni A pattern, so-called cellular neurilemoma, for a malignant lesion. The latter consideration was particularly relevant in respect of case 1, but in that instance the clinical course provided more than sufficient corroboration of the histological diagnosis. Absence of a capsule and a clearly defined, smooth tumour surface was noted in all three cases and was taken as evidence of an invasive property. Electron microscopy in respect of cases 1 and 2 revealed prominent nucleoli in many tumour cells, and this also is suggestive of malignancy.

CLINICAL COURSE

Although only 13 well documented cases of orbital malignant peripheral nerve sheath tumours have been reported, previous authors¹⁰ have stressed the

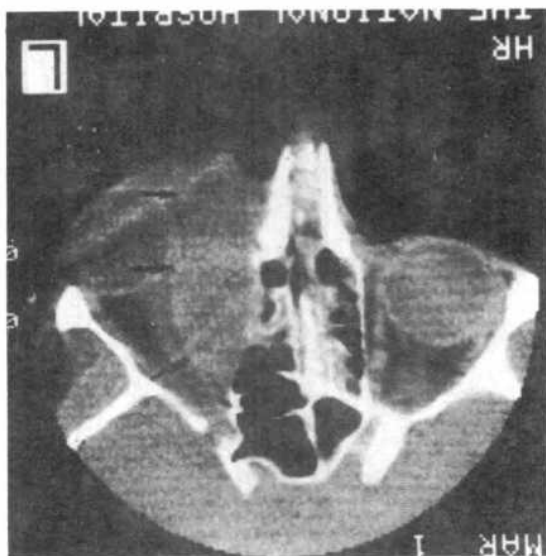


Fig. 7 Patient 3. An axial CT scan shows a large mass (arrows) filling the medial orbit extending from the skin anteriorly almost to the orbital apex. The medial wall of the orbit appeared intact.

tendency for this tumour to arise from the supra-orbital branch of the trigeminal nerve (10 cases). Mortada¹ described an inferotemporal orbital malignant neurilemoma (for which the nerve of origin was not specified), and in our patients the tumour arose from the infraorbital nerve in one and intraconally in another. In the third patient the tumour site was compatible with origin from a medial branch of the ophthalmic division of the trigeminal nerve.

At presentation there is frequently a history of a pre-existing rather innocuous lump, often situated above the medial canthus (as in patient 3), which some patients related to previous trauma³ or which is related to generalised neurofibromatosis (reported in four cases; none of our patients had stigmata of neurofibromatosis). There may have been previous attempts at excision with recurrence after three to nine months (patients 1, 3, and Schatz²). The repeated attempts at excision of a benign lesion later complicated by sudden spontaneous enlargement (patient 1) is suggestive of malignant change in a previously benign lesion, as reported by Schatz.²

The radiological features of these lesions have not been helpful in establishing or even suggesting the diagnosis. In patient 1 enlargement of the infraorbital canal was suggestive of a nerve tumour, but the circumscribed homogeneous masses seen on CT scans in patients 2 and 3 were non-specific. The hyperaemia of the tumour noted on angiography in patient 2 coupled with the relatively short history

suggested the erroneous diagnosis of haemangiopericytoma. Neither of the other cases had such a profuse blood supply.

These tumours behave in an aggressive manner, with extension along the involved nerve into the middle cranial fossa or metastasis to preauricular, submandibular, or cervical lymph nodes³ or to distant sites such as lungs and mediastinum (four reported cases) or liver (one reported case). The prognosis is therefore poor. Of 13 cases reported, nine died of their disease within five years. In two further cases follow-up was of nine months or less, and two patients have survived five and seven years respectively.

As peripheral nerve sheath tumours are radio-resistant,^{10,11} the only treatment capable of producing a cure is total excision. This may be feasible if the lesion is confined within the orbit. Frozen sections may be used to ensure the nerve margins are free of tumour.¹² However, owing to the tendency of these tumours to spread rapidly along the nerve sheath into the subarachnoid space,² nerve involvement through the superior orbital fissure into the middle cranial fossa is frequently noted at the time of orbital surgery (patients 1, 2, and Grinberg and Levy³). Radical midfacial surgery combined with exploration of the middle cranial fossa then offers the only hope of total excision. Often, as in our first patient, this may not be possible.

Fortunately these tumours are very uncommon, but ophthalmologists should be aware that, when they do occur in the orbit, early diagnosis and extensive surgical intervention may be needed to effect a cure.

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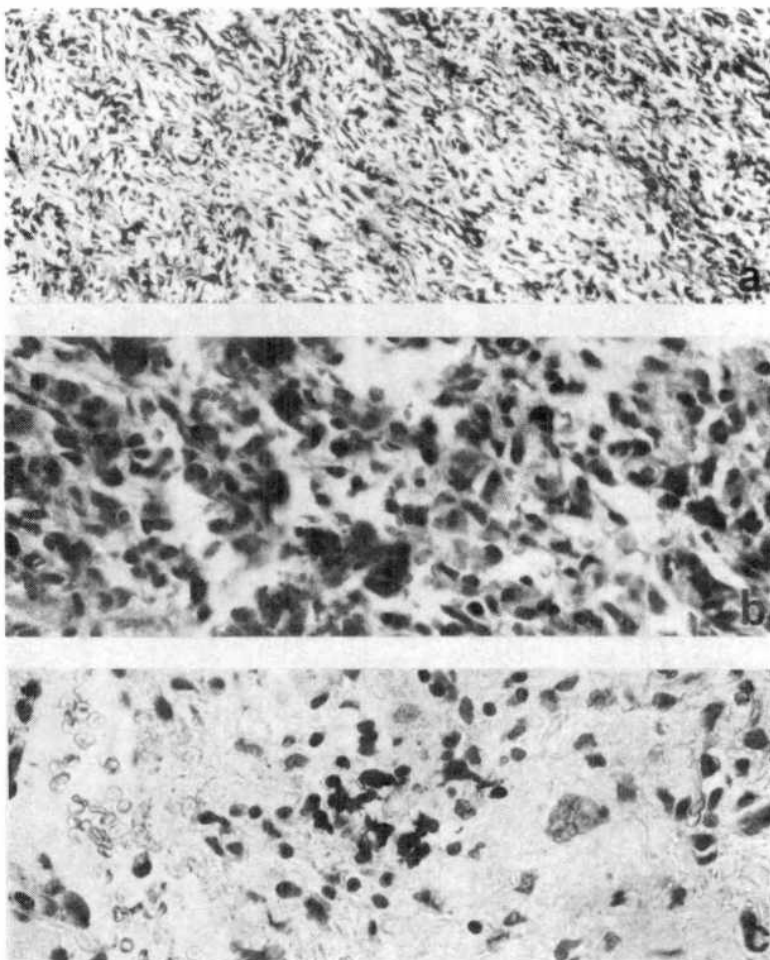


Fig. 8 Patient 3. (a) The tumour consists of spindle cells distributed in a loose and somewhat haphazard fashion. (Glees and Marsland, $\times 125$). (b) In places the cells have unusually large, hyperchromatic nuclei. (Haematoxylin and eosin, $\times 313$). (c) Clusters of cells which react positively for S-100 protein are extremely sparse. (Immunoperoxidase, $\times 125$).

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Local extraocular extension of retinoblastoma following intraocular surgery

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SUMMARY Three cases of local extraocular extension of retinoblastoma following intraocular surgery via a transscleral approach have been seen in one centre during a 12-month period. This number represents a significant increase on the previous incidence of this serious complication, which may be related to more widespread use of vitrectomy techniques. Orbital and local lymph node recurrence of retinoblastoma have been associated with a very poor survival rate in the past, and steps must be taken to limit the chance of this happening should an intraocular surgical procedure be performed inadvertently on an eye containing a retinoblastoma. Early enucleation without implant is advised, and adjuvant orbital radiotherapy is strongly recommended, even when there is no histopathological evidence of local extraocular tumour spread.

Retinoblastoma is the most common primary intraocular tumour of childhood, with an incidence of between 1 in 14 000 and 1 in 34 000 live births.¹ The average age at diagnosis is 18 months. Bilateral cases usually present earlier, at a mean age of 12 months but rarely present after age 5 years. Unilateral cases usually present at a mean age of 23 months but may occur well into the teens.²

Retinoblastoma presenting late is often misdiagnosed as intraocular inflammation. Misdiagnosis may lead to intraocular surgery in an attempt to confirm an inflammatory or other cause or in an attempt to improve vision. This results in a delay in establishing the correct diagnosis, which, in allowing tumour growth to continue unabated, predisposes to extraocular spread either by direct extrascleral extension or via the severed end of the optic nerve.³

Intraocular surgical procedures have a more direct and serious adverse effect on survival rate in retinoblastoma, because they predispose to local extraocular spread by breaching the natural barrier provided by the sclera or cornea. Extraocular spread alone is an adverse prognostic factor, but when it leads to orbital recurrence or local lymph node metastasis the mortality rate is extremely high.⁴

We report three cases of retinoblastoma in older children referred to a specialist centre for

management of orbital recurrence or local lymph node metastasis. In all three the diagnosis of retinoblastoma had not been suspected initially but had been made on the results of intraocular biopsy.

Case reports

CASE 1

An 8-year-old girl was referred for treatment of a mass in her enucleated right socket.⁵ She had initially presented in April 1986, then aged 7, with a one-month history of a red right eye and decreased vision. She was found to have cells in the anterior chamber, iris nodules, vitreous opacities, and retinal exudates with a secondary glaucoma. The left eye was normal. A presumptive diagnosis of panophthalmitis had been made and the initial treatment was with topical steroids and acetazolamide, to which she showed no response.

In July 1986, four months after presentation, she underwent a right pars plana lensectomy in an attempt to improve her vision. During surgery she was noted to have an area of white friable tissue overlying the inferior pars plana. Cells from this area were aspirated and found to be highly suspicious of retinoblastoma. Three weeks later the right eye was enucleated and an Allen orbital implant inserted.

Histological examination of the globe revealed poorly differentiated retinoblastoma almost confined

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Fig. 1 Tilting of the ocular prosthesis in case 1.

to the anterior segment in the form of diffuse infiltration of the iris and ciliary body. Seeding of the anterior vitreous was also present, but the retinal component of the tumour was confined to the anterior periphery. The severed end of the optic nerve was not affected, and there was no choroidal invasion. She received no further treatment post-operatively.

Six months after enucleation she presented with tilting and forward displacement of her right prosthesis with a rapid increase in orbital swelling and pain, and was referred for specialist management (Figs. 1, 2). High resolution CT scanning showed enhancing tissue in the right orbit but no evidence of intracranial tumour. Cytological study of material obtained by bone marrow aspiration and trephine showed no evidence of malignant infiltration by standard histological techniques, but a few cells were positive to testing with a monoclonal antibody against neuroectoderm (UJ13A). Cytological examination of the cerebrospinal fluid (CSF) showed no evidence of disseminated retinoblastoma.

In March 1987 an excision biopsy of the right orbital mass was performed, revealing undifferentiated retinoblastoma extending to the margins of resection. A biopsy of the posterior orbit was free of tumour. Review of the histology of the enucleated eye at this stage showed a few tumour cells in the sclera in a haemorrhagic area presumed to correspond to the initial biopsy site. The patient then received radiotherapy to the right orbit, 4400 cGy (44 Gy) in 22 fractions over 30 days, and six courses of chemotherapy with vincristine, cyclophosphamide, cis-platinum, and etoposide, with intrathecal methotrexate. She remained free of disease 21 months after her orbital recurrence.

CASE 2

A 5-year-old girl was referred for management of a preauricular lymph node metastasis of retinoblastoma following enucleation of her right eye three months earlier. She had presented initially, two weeks after minor trauma to her right eye in September 1985, with decreased vision, a right divergent squint, and

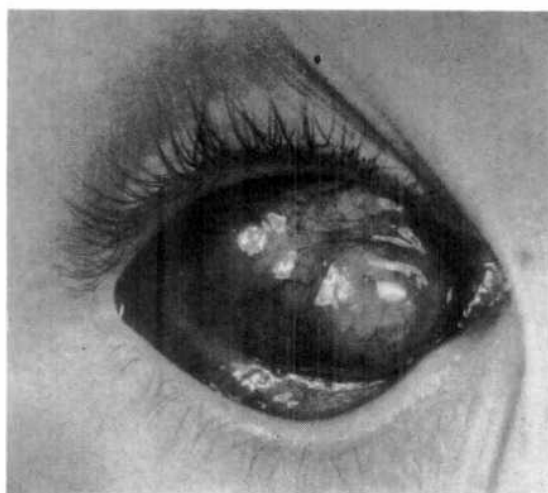


Fig. 2 Orbital recurrence of retinoblastoma in case 1.

heterochromia. She was noted to have rubeosis iridis, and some white, solid-looking lumps associated with vitreous haemorrhage were seen behind a clear crystalline lens. A CT scan showed no evidence of an intraocular foreign body or mass lesion. A B scan ultrasound of the right eye showed a very dense vitreous opacity with no evidence of a solid mass. No mention was made of any intraocular calcification. One month later a right vitreous biopsy was performed.

Histological examination of the specimen showed clumps of cells with basophilic nuclei which were thought to be malignant. In December 1985 she underwent a right enucleation and acrylic ball implant. Histological examination of the enucleated globe showed retinoblastoma infiltrating the optic nerve, though the cut end of the nerve was free of tumour. There was no substantial choroidal invasion by the tumour, and no comment was made on the appearance of the sclerostomy site. No further treatment had been given after enucleation.

Three months later she presented again with an enlarged right preauricular node and was referred for further treatment. A lymph node biopsy showed retinoblastoma, though no tumour mass could be demonstrated in the right orbit by CT scan. Systemic staging investigations including bone marrow aspiration and trephine and cytological examination of the CSF were negative for disseminated retinoblastoma. She was treated with radiotherapy to the right parotid region to a total dose of 4000 cGy in 20 fractions over 28 days. Microscopic residual orbital tumour was presumed to be present, and the right orbit was included in the treatment field. Radiotherapy was followed by six courses of chemotherapy



Fig. 3 Section of the sclerostomy site in case 3 to show prolapsing necrotic tumour tissue. (H and E, $\times 22$).

as in the first case. She remained free of tumour 18 months later.

CASE 3

This 6-year-old girl was referred for management of orbital recurrence of retinoblastoma. She had presented initially with leucocoria in the right eye. A tentative diagnosis of Coats's disease had been made, but she subsequently underwent a biopsy which was performed beneath a partial thickness scleral flap. The histological diagnosis proved to be retinoblastoma. Four days after the biopsy she underwent a right enucleation. Histological examination of the enucleated eye showed a poorly differentiated retinoblastoma with choroidal invasion. There was extension of the tumour into the optic nerve head, no comment being made about the severed end of the nerve. There was a large gaping scleral perforation through which necrotic tumour tissue had prolapsed (Fig. 3). No further treatment had been given after enucleation.

In October 1986, three months later, she presented with an orbital recurrence of the tumour and was referred for specialist management. Excision biopsy of the orbital mass was positive for retinoblastoma. Systemic staging investigations were negative for disseminated retinoblastoma, and she underwent

radiotherapy to the right socket, receiving 4500 cGy in 23 fractions over 37 days, and six courses of chemotherapy as detailed previously. She remained free of disease 11 months later.

Discussion

Three cases of orbital or local lymph node metastasis of retinoblastoma presenting to a specialist centre during a 12-month period are described. An intraocular operation had been performed in all three cases prior to the establishment of the diagnosis of retinoblastoma, and none of the cases had received any specific treatment directed towards reducing the likelihood of subsequent orbital recurrence.

Orbital or local lymph node recurrence of retinoblastoma is uncommon. In one large series from the same specialist centre only 16 cases were reported among 317 children referred during a 15-year period between 1970 and 1984.⁴ Only one of these 16 had undergone intraocular surgery prior to the diagnosis of retinoblastoma being established. The present group of patients is consecutive with that previously reported and represents a substantial increase in the number of cases with intraocular procedures performed prior to enucleation. This increase from one case in 16 years to three cases within one year is

alarming and may be related to new and more widely available technology in vitreous surgery.

Orbital or lymph node recurrence of retinoblastoma is a very serious event. Only one of the 16 cases previously reported from this centre is a long-term survivor.⁴ This child was free of disseminated retinoblastoma on systemic staging and was treated with a combination of excision biopsy of an orbital recurrence, radical orbital radiotherapy, and systemic adjuvant chemotherapy. This was the index case on which the management plan chosen for the three children herein described was based. Although all three patients have sustained clinical remissions following this treatment, they cannot yet be counted long-term survivors.

Although retinoblastoma usually presents before the age of 5 years, sporadic, unilateral, unifocal retinoblastoma may occur well into the teens. Even in the older child the diagnosis of retinoblastoma must be considered in any case of unilateral leucocoria with signs of intraocular inflammation. The advantages of achieving a tissue diagnosis of an intraocular inflammatory condition by intraocular biopsy must be set against the very serious consequences of releasing tumour cells into the orbit if the diagnosis proves to be one of retinoblastoma.

Rodriguez⁶ has reported examples of tumour seeding along 19-gauge needle tracks at three and six weeks after biopsy. He suggests that extraocular extension of the tumour is more likely to occur if enucleation is delayed or if the entry site of the instrument is immediately beneath the bulk of the tumour. Transcorneal aqueous aspiration has been used for many years as an aid to the diagnosis of retinoblastoma with anterior segment involvement.⁷ The method carries the theoretical advantages that the entry site is not subconjunctival, so that it can be easily observed for signs of tumour recurrence and deep orbital seeding of the tumour is unlikely. Nevertheless superficial conjunctival implantation of tumour cells may occur, and any affected conjunctiva might not be removed during enucleation. The risk of extraocular seeding of retinoblastoma following a breach of scleral or corneal barrier has long been recognised. 'It is questionable if it is legitimate to aspirate the subretinal fluid for diagnostic purposes since any escape into the orbit may lead to extraocular spread; and it is certainly illegitimate to puncture the vitreous, a procedure which has led to rapid fungation into the orbit.'⁸

If a diagnosis of retinoblastoma is made as a result of an intraocular biopsy, vitrectomy, or lensectomy, strenuous efforts should be made to limit the chance of orbital recurrence. It is recommended that the affected eye should be enucleated as soon as possible and subjected to detailed histological examination, with particular attention being paid to the sclerostomy sites. The enucleated socket will require frequent examination, and to facilitate this an orbital implant should not be inserted. Of eight patients in whom histological examination of the enucleated eye revealed evidence of local extraocular spread of retinoblastoma and who received orbital radiotherapy soon after enucleation, none had recurrence in the orbit.⁴ Adjuvant orbital radiotherapy is therefore advised in the presence of local extraocular extension and may be a wise precaution even if tumour cells cannot be detected histologically at the sclerostomy site.

In summary, we advise that, when intraocular surgery is inadvertently performed on an eye containing a retinoblastoma, enucleation should be performed as soon as possible, without insertion of an orbital implant. Even if systemic staging investigations show no evidence of disseminated retinoblastoma, adjuvant orbital radiotherapy should be begun in the early postoperative period.

Dr J Harry kindly provided histological slides of case 3 for further study. We thank Mr C M P Claoue for helpful discussion, and Walter for secretarial help.

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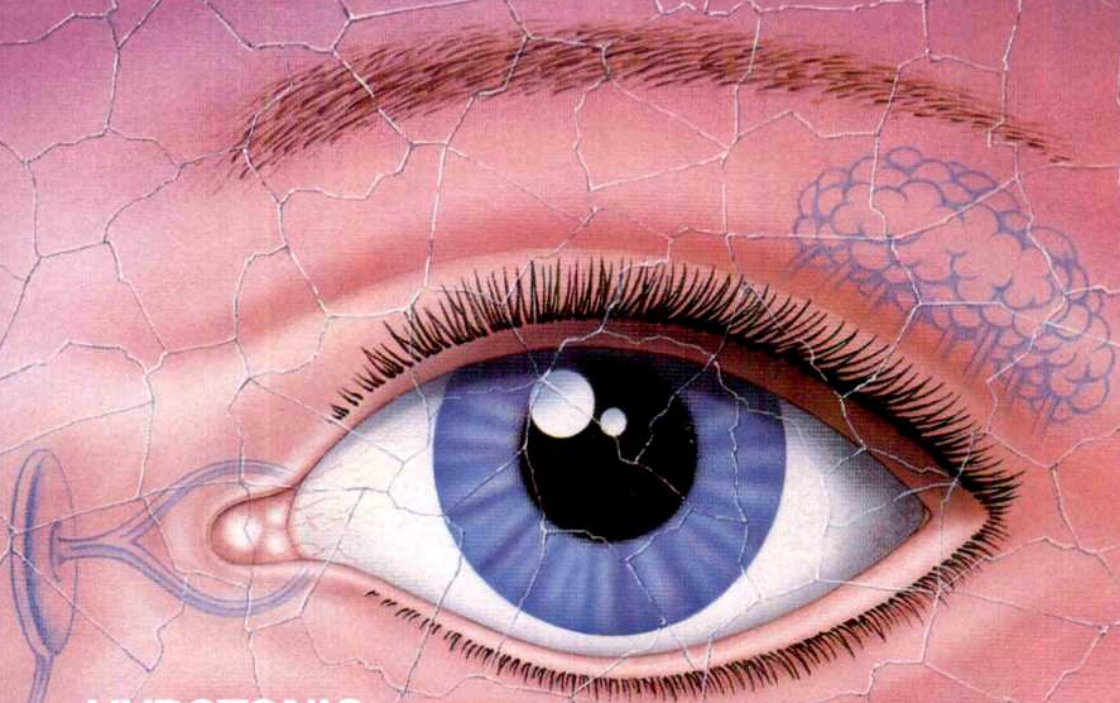
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ALLERGAN PHARMACEUTICALS

SCIENCE WITH VISION

Cyclosporin therapy for severe scleritis

DENIS WAKEFIELD¹ AND PETER McCLUSKEY²

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SUMMARY To ascertain the efficacy of systemic cyclosporin therapy in the management of scleritis we performed an open, uncontrolled study of the use of this drug in severe refractory disease. Five of seven patients whose disease had previously been poorly controlled with a combination of corticosteroids and immunosuppressive drugs responded to cyclosporin therapy (10 mg/kg/day). Systemic side effects occurred in all but one patient, with tremor, hirsutism, hypertension, and raised serum creatinine being common. Recurrence of disease activity on decreasing the dosage of cyclosporin was frequent. The results indicate that cyclosporin is a useful additional drug in the treatment of severe scleritis.

Scleritis is a severe, potentially sight threatening, inflammatory disease involving the ocular surface. Despite recent advances its treatment remains a difficult problem. Systemic immunosuppressive therapy with corticosteroids or immunosuppressive agents or both is usually required to control the disease.¹ Early therapeutic intervention is important to prevent ocular complications and to minimise the potential morbidity and mortality associated with underlying systemic disease.

Systemic corticosteroids in high dosage, either orally or in intravenous pulses, are widely accepted as an effective form of treatment in patients with severe scleritis.^{2,3} But this treatment is often associated with unacceptable side effects and does not always control scleral inflammation. The addition of immunosuppressive agents in patients with severe scleritis improves the ocular outcome and decreases the morbidity associated with systemically administered corticosteroids.⁴ Azathioprine, cyclophosphamide, and cyclosporin have previously been reported to be effective and safe in the management of severe ocular inflammation.^{2,5} We and others have reported the successful use of cyclosporin in the treatment of patients with a variety of ocular inflammatory syndromes resistant to other immunosuppressive

regimens.^{6,7} In the present study we report the therapeutic effect of cyclosporin in the treatment of severe scleritis.

Patients and methods

Seven patients with scleritis were referred for assessment and treatment of their disease to the Ocular Immunology Clinic at St Vincent's Hospital. All seven patients were examined by the authors before and during their treatment and were followed up at regular intervals. They were also assessed by an ophthalmologist and an immunologist. A detailed history was taken and physical examination performed as well as appropriate investigations to exclude the presence of an associated systemic disease. Prior to treatment all patients had active ocular disease and were receiving a variety of topical and systemic anti-inflammatory drugs. These had either failed to control the disease and/or were associated with unacceptable side effects.

All patients were started on cyclosporin 10 mg per kilogram body weight daily. After two to four weeks of therapy the dose of cyclosporin was incrementally decreased at one- to two-week intervals until a dose of 5 mg/kg or less was reached in each patient. Pulse methylprednisolone or oral steroids were continued at the current dose and other immunosuppressive agents were stopped. Pulse steroids were then

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Table 1 Clinical features of patients with scleritis

Patient age/sex	Diagnosis	Duration (months)	Systemic association	Treatment complications prior to cyclosporin therapy
1/44/F	Necrotising scleritis	6	Nil	Diabetes
2/65/M	Necrotising scleritis	13	Nil	Anaemia
3/58/F	Necrotising scleritis	24	Polyarteritis nodosa	Diabetes
4/48/F	Necrotising scleritis	19	Nil	Hypertension
5/66/M	Necrotising scleritis	27	Nil	Osteoporosis
6/52/F	Necrotising scleritis	12	Nil	Cushingoid
7/67/F	Necrotising scleritis	14	Nil	Alopecia
				Leukopaenia
				Diabetes
				Hypertension

Duration was defined as the time from the onset of symptoms until cyclosporin therapy was begun.

Table 2 Previous treatment

Patient	Drug	Dosage	Duration (months)
1	Methylprednisolone	1 g-125 mg/dose	4
	Azathioprine	150 mg/day	3
2	Prednisolone	10-50 mg/day	2
	Methylprednisolone	1 g-250 mg/dose	5
	Cyclophosphamide	150 mg/day	3
3	Prednisolone	5-50 mg/day	3
	Methylprednisolone	1 g-250 mg/dose	4
	Azathioprine	150 mg/day	4
	Cyclophosphamide	150 mg/day	3
4	Prednisolone	0-50 mg/day	2
	Methylprednisolone	1 g-250 mg/dose	3
	Azathioprine	150 mg/day	2
	Cyclophosphamide	100 mg/day	3
5	Methylprednisolone	1 g-125 mg/dose	6
	Cyclophosphamide	100-200 mg/day	3-5
6	Prednisolone	0-100 mg/day	2
	Azathioprine	100-150 mg/day	2
7	Prednisolone	0-100 mg/day	14
	Methylprednisolone	1 g-125 mg/dose	4
	Azathioprine	150 mg/day	4

Methylprednisolone was used as intermittent intravenous pulse therapy.

reduced according to our published protocol.¹ Treatment was initiated in several patients while they were in hospital for investigation and stabilisation of the disease.

A subjective grading system,⁵ analogous to that previously described for patients with uveitis and retinal vasculitis was used. A scleritis score was calculated when the patients first presented and at each follow-up visit. Improvement was defined as a decrease in the total score of greater than 2 and resolution at a total score of less than or equal to 4.

Table 3 Scoring system for severity of scleritis

Clinical feature	Clinical grading	Score
1 Location	Unilateral	1
	Bilateral	3
2 Tenderness	0-4+	0-4
3 Nodules	Single	2
	Multiple	4
4 Scleral necrosis	Absent/quiescent	0
	Present	2
	Progressive	4
5 Visual acuity	Initially $\leq 6/18$ or decrease by 2 or more lines	1
6 Anterior chamber cells	0-4+	0-4
7 Raised IOP	> 22 mm Hg	1
8 Vitreous cells	0-4+	0-4
9 Retinal detachment	Absent	0
	Present	4

Improvement: a decrease in the scleritis score of 2 or more points.

Resolution: a decrease in the scleritis score to 4 or fewer points.

Each eye is scored separately. In bilateral disease the higher total score is used.

IOP=intraocular pressure.

Table 4 Scleritis score in patients treated with cyclosporin

Patient	Pretreatment scleritis score	Scleritis score at three months
1	12	4
2	10	9
3	12	3
4	9	3
5	13	13
6	10	3
7	12	3

Results

The clinical features of the patients are summarised in Table 1. There were five females with a mean age of 53.8 (SD 8.06) years and two males with a mean age of 65.5 (SD 0.5) years. Of the seven patients one had an associated systemic disease, polyarteritis nodosa, which was diagnosed by satisfying previously published criteria. The treatment regimen for each patient is summarised in Table 2. The scleritis scoring system is detailed in Table 3, and Table 4 summarises the scleritis score for each patient at presentation and at twelve weeks after the commencement of treatment. In five patients there was a significant decrease in the scleritis score at six weeks. This decrease in the scleritis score was maintained over the subsequent observation period. The mean duration of treatment was 7.4 (SD 2.4) months.

Table 5 summarises the present clinical status, complications of treatment, and duration of follow-up. The mean duration of follow-up was 8.4 months, with a minimum of four months. Cyclosporin was

Table 5 Results of treatment with cyclosporin

Patient	Duration of treatment (months)	Result	Duration of follow-up (months)	Complications
1	4	Remission	4	Tremor
2	5	Relapse, enucleation	7	Tremor, creatinine*
3	8	Remission	13	Creatinine,* hirsutism
4	10	Remission	12	Tremor, hypertension
5	11	Relapse	11	Facial pain
6	6	Remission	8	Tremor, hypertension
7	8	Remission, relapse	4	Tremor, creatinine,* hirsutism, gum hypertrophy

Duration of follow-up was defined as the time from the start of cyclosporin therapy to the present.

*Increase above upper limit of normal.

well tolerated by all but one patient, and only one patient developed side effects that warranted the cessation of therapy. The most common side effects were hirsutism, gum hypertrophy, tremor, hypertension, and mild nephrotoxicity. There were no associated opportunistic infections.

Three patients suffered a relapse in their scleritis on attempted withdrawal of cyclosporin. In patients 2 and 5 disease activity recurred when the cyclosporin dosage was decreased below 5 mg/kg/day, while patient 7 relapsed when the cyclosporin dose was decreased to 3 mg/kg/day. In each case patients were treated with intravenous pulse methylprednisolone therapy and the cyclosporin dosage was increased to 10 mg/kg/day. Patients 5 and 7 responded to this medication with a significant improvement in symptoms and decrease in their scleritis score. Unfortunately patient 2 suffered a perforation of the globe in an area of extensive scleral necrosis and corneal thinning. There was severe disorganisation of the anterior segment and it was decided that enucleation was the most appropriate form of therapy.

There was no difference in clinical features, scleritis score at presentation, or complications between patients who responded to cyclosporin and those who failed to respond to this treatment.

Discussion

Five of the seven patients treated as part of this uncontrolled trial responded to the use of cyclosporin. All had been previously treated with a variety of immunosuppressive agents which had failed to

give adequate disease control or were associated with unacceptable side effects. There was no difference between responders and non-responders to treatment with cyclosporin in terms of their previous treatment, associated disease, or scleritis score at presentation.

Cyclosporin has been increasingly recognised as an effective therapeutic agent in the management of a variety of autoimmune diseases.⁸ Inflammatory eye disease, particularly uveitis, is often well controlled by the regular use of systemic cyclosporin.⁷ The results of the present study indicate that cyclosporin is an effective additional agent in the management of the majority of patients with severe scleritis refractory to other forms of therapy.

Cyclosporin represents the prototype of a new class of drug that appears to work, at least in part, by acting at the level of cytokine production by immune cells.⁹ The selective ability of cyclosporin to interfere with the action of interleukin-2 makes it an appropriate agent for the treatment of diseases believed to be mediated by T cells. Although the immunopathogenesis of scleritis is not fully understood, it is believed to be due to immune complex mediated vascular damage to scleral vessels, with the subsequent generation of a granulomatous reaction.⁵ T cells have an essential role in the formation of such granulomas, and cyclosporin may act in part by decreasing this component of the inflammatory response.

The widespread use of cyclosporin in the treatment of autoimmune disease has been limited by a concern for the potential side effects, especially its propensity to cause renal, hepatic, and lymphoproliferative disease. This study provides further evidence that such systemic side effects appear to be less prevalent in patients with inflammatory eye disease, in whom severe adverse reactions appear to be less frequent, than those seen in patients treated to prevent organ rejection following transplantation.⁷ Tremor, hirsutism, hypertension, and raised creatinine levels were all observed complications in our patients. Another problem associated with the use of cyclosporin was the propensity for the scleritis to relapse on attempted withdrawal of the drug. This has been previously observed in the treatment of other autoimmune diseases with cyclosporin and is not always preventable by slowly withdrawing the drug.

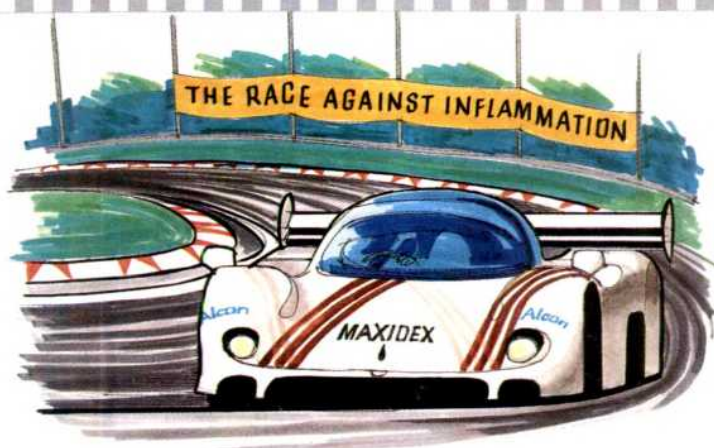
The results of the present study indicate that cyclosporin is a potentially useful drug in the treatment of severe scleritis refractory to other immunosuppressive regimens. Unfortunately it is not universally effective, is complicated by frequent, mild side effects, and may be associated with recurrence of disease on attempted drug withdrawal. Despite these limitations we consider that cyclosporin is a useful

additional drug in the management of severe scleritis, and its therapeutic value in the treatment of this disease warrants further investigation.

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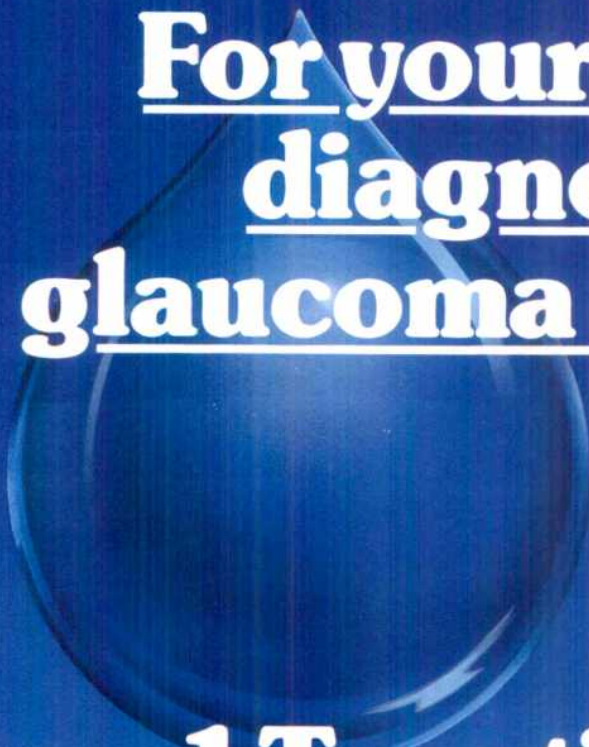
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Kitazawa, Y. et al. Acta XXIV International Congress of Ophthalmology, 1983; P. Henkind (Ed.), Lippincott, Philadelphia.

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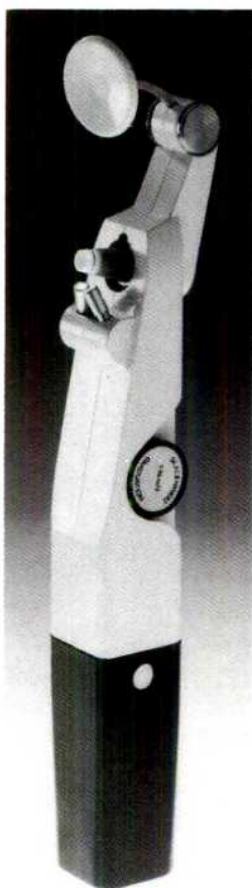
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Nasal versus temporal preretinal vasoproliferation in retinopathy of prematurity

I NISSENKORN, I KREMER, S COHEN, AND I BEN-SIRA

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SUMMARY Nasal preretinal neovascularisations have been observed to develop at least two weeks earlier than those on the temporal side in more than a third of premature babies with retinopathy of prematurity (ROP) stage 3, weighing between 690 and 1030 g. All these babies were assigned for cryotherapy. This interesting observation is discussed in relation to retinal vascular development and the pathogenesis of ROP.

The embryonic retina remains avascular until the fourth month of fetal development.¹⁻³ At 4 months spindle cells are found in Bergmeister's precapillary cone surrounding the walls of the hyaloid artery and its veins.³ From the walls of the venous channels on either side of the hyaloid artery the spindle cells undergo active mitosis and begin their migration into the nerve fibre layer at the 16th week of embryonal life.⁴ These undifferentiated spindle cells continue to advance towards the ora serrata, so that they always form the peripheral margin (vanguard) of the developing capillaries.^{5,6} The capillary bed with the vanguard of spindle cells appears to spread centrifugally, so that by the eighth fetal month the primitive capillary network extends almost to the ora serrata nasally but only to the equator temporally.^{1,3,4} It is therefore obvious that through all stages of retinal development the avascular area of the developing temporal retina is much larger than the avascular area of the nasal retina. Consequently we should expect that in stage 3 retinopathy of prematurity (ROP) the active neovascular proliferations would be much more extensive and appear earlier in the temporal retina than in the nasal retina.

We present here an interesting observation on the development of nasal versus temporal vasoproliferative disease in ROP stage 3, found in premature babies born between the 26th and 28th weeks of gestation and with a birth weight less than 1250 g.

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Materials and methods

During the years 1985-7, 85 premature babies weighing under 1250 g, born at the age of 28 weeks or less, were examined in the Neonatal Intensive Care Unit (NICU). The first fundus examination was performed at the age of 3 to 4 weeks. When the avascular area was found to be located in Zone I or II, the subsequent examinations were performed at least once a week. When ROP stage 3 (moderate) was diagnosed, cryotreatment was performed according to a protocol described by Ben-Sira *et al.*^{7,8}

Results

Seventeen out of 85 premature babies (20%) were found to have ROP stage 3 and subsequently underwent cryotherapy. In six of the 17 cryotreated babies (35%) with ROP stage 3 the vasoproliferative disease was found to begin at least two weeks earlier in the nasal side of the retina than the temporal side (Table 1). Five of the six babies weighed less than 1000 g and one weighed 1030 g. In five babies cryotherapy was performed first on the nasal retina and subsequently, owing to progression of the active vasoproliferative disease temporally, on the temporal side. In only one baby was the vasoproliferative disease confined to the nasal retina, while ROP stage 2 only was noted on the temporal side (Table 1). Cryotherapy was therefore applied to the nasal avascular retina and not to the temporal side. No difference was found in the

Table 1 Timing and extent of nasal versus temporal ROP stage 3

Case	Weight (g)	Gestational age (weeks)	Eyes	ROP timing (weeks after birth), stage 3	
				Nasal side	Temporal side
1	750	26	Both	4	6
2	1030	27	Both	6	8
3	990	28	Both	4	7
4	690	28	Both	5	8
5	910	26	Both	6	8
6	860	27	Both	6	7*

*Stage 2 only.

clinical course of ROP stage 3 whether it started in the nasal retina or the temporal. Moreover, vasoproliferative disease in the nasal retina was found to regress after cryotherapy in the same manner as it did on the temporal side.

Discussion

Cogan⁹ and Patz¹⁰ have shown that at 8 months of embryonic life the retina is completely vascularised only in the nasal periphery, whereas the temporal periphery is not completely vascularised until shortly after birth of the full-term infant. At the embryonal age of 8 months the developing capillaries have just reached the equator in the temporal retina (Fig. 1). Since the temporal periphery is the last part of the retina to become vascularised, the temporal retina has larger ischaemic areas than the nasal retina.³ This pattern of vascularisation probably explains the greater susceptibility of the temporal retina to ROP and may even explain the occasional case of ROP occurring in the full-term infant's temporal retina.¹¹

Extensive animal studies have shown that the retinal vessels are susceptible to oxygen damage only when the retina is incompletely vascularised.¹²⁻¹⁵ In addition the premature baby's retinal vasculature was found to be vulnerable to many other noxious factors which may be associated with ROP.¹⁵⁻¹⁸

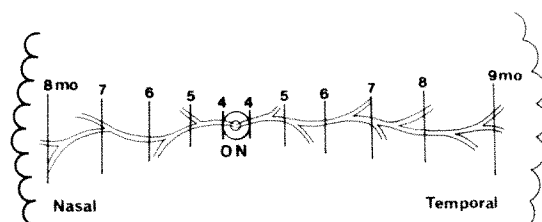


Fig 1 Relationship between retinal vascular development and retinal topographical anatomy. ON = optic nerve.

We would therefore expect that a premature baby born before the 28th week of gestation, and weighing less than 1250 g, would develop more extensive ischaemic vasoproliferative disease, and much earlier on the temporal than the nasal retina. It is an interesting fact that in more than a third of the cases reported here (35%) ROP stage 3 with confluent preretinal neovascularisation developed at least two weeks earlier in the nasal retina than the temporal. All these babies except one weighed less than 1000 g. Later on, following cryoablation of the nasal retina, the vasoproliferative disease progressed to the temporal side, and was subsequently treated by further cryoablation in all babies except one. In the last baby ROP of the temporal retina remained at stage 2, and there was therefore no indication for cryotherapy. In agreement with our findings, Fielder *et al* reported that the first visible changes of acute ROP can often be found in the nasal retina, particularly in the more immature baby.¹⁹⁻²¹

Unfortunately we cannot find any firm explanation for this unexpected observation. It should be stressed that ROP is a multifactorial disease,^{18, 21} whose pathogenesis is still incompletely understood. It may well be that peripheral retinal avascularity and subsequent ischaemia are not the only pathogenic factors. According to other hypotheses, such as the 'spindle cell theory'²² as well as that of tissue oxygen radicals,^{18, 21} the temporal retina should have no priority as the 'place of less resistance.'

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The Briard dog: a new animal model of congenital stationary night blindness

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SUMMARY Congenital stationary night blindness (CSNB), apparently inherited in an autosomal recessive manner, was observed in a litter of Briard dogs in Sweden. Of nine litter mates five had nyctalopia. The results of different clinical tests, including electroretinography (ERG), were compared with the results found in four human cases of CSNB, three of which were most probably associated with autosomal recessive inheritance and one with X-linked inheritance. The congenital and stationary nature of the disease, ophthalmoscopically normal appearing fundi, and recordable but reduced photopic flicker responses were some of the similarities found between canine and human cases. The single-flash ERG response was abnormal in the humans as well as in the affected Briards. However, the human cases showed a 'negative' ERG, whereas in the Briards both the a and b waves were extremely reduced and present only at a photopic level. Cases similar to these Briards have been described also in man, where rhodopsin concentration and regeneration were found to be normal, suggesting a disturbed transduction mechanism. It thus appears that the Briard dog may become a valuable model of human CSNB.

A group of retinal disorders in man known collectively as congenital stationary night blindness (CSNB) is mainly characterised by a normal fundus appearance, loss of scotopic function, and an abnormal electroretinogram (ERG).¹ Though not very common, it was first described over 300 years ago as a dominant disease in the Nougaret family in France.² Three modes of genetic transmission have since been described: a dominant form, an autosomal recessive form,³ and a sex linked recessive type.⁴

Two types of CSNB have been differentiated by means of the ERG. In the first type, described by Schubert and Bornschein,⁵ the dark-adapted response is characterised by a normal or slightly subnormal a wave, while there is no (or perhaps a minimal) scotopic b wave above baseline. This 'negative type' of ERG or type 1 ERG, is the most common type of ERG in CSNB. In the type described by Riggs⁶ the a and b waves are proportionally more reduced, and the amplitudes may vary substantially (type 2 ERG). In some cases only reduced

photopic responses could be recorded from the dark-adapted retina. There seems to be no correlation between these two ERG types and the mode of inheritance of CSNB.^{1,7–10} Recently, the Schubert-Bornschein type of CSNB has been further subdivided, mainly on the basis of ERG findings and psychophysical testing, into the complete type, which completely lacks rod function, and the incomplete type with some remaining rod function.⁷ Furthermore, in all forms of CSNB the implicit times for scotopic and photopic b waves were found to be almost the same,¹ whereas in normal persons the implicit time of the scotopic b wave is at least twice as long as that of the photopic b wave.

Although the cause of CSNB is still not clear, the results of ERG and fundus reflectometric studies have contributed to our understanding of the disease. Carr and associates showed that both the concentration and regeneration of rhodopsin were normal in two cases of CSNB affected human retinæ.¹² One of the cases showed a 'negative' ERG, and in the other only a minimal photopic response could be elicited. It seems that the first case represents a defective transmission from the rods to the inner retina and

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that the second case involves a failure in the transduction process at some point between the initial event and the change in plasma membrane potential.¹²⁻¹⁴ The few CSNB affected eyes that have been examined histologically have not shown any morphological alterations by either light or electron microscopy.^{15,16} Female carriers of X-linked recessive CSNB have shown reduced oscillatory potentials.¹⁷

The pathophysiology of specific retinal disease processes in man may be elucidated by study of animal models with similar defects. A form of night blindness with similarities to the Schubert-Bornschein type of CSNB was reported in the Appaloosa horse.¹⁸ In this animal the trait was recessively inherited and there was behavioural evidence that the animals were night-blind. Electrophysiologically only the a wave of the ERG was recordable. Histological studies of one nyctalopic horse showed a normal retina. Transmission densitometry of an isolated retina revealed an ample supply of rhodopsin.¹⁴

In the dog recent reports of sporadic cases of night-blind Briards have been obtained, mainly from France (Lescure F, personal communication, 1987) as well as from the USA (Ris RC, Aguirre GD: The Briard problem. Unpublished; for abstract see *Transactions of the Fourteenth Annual Scientific Program of the College of Veterinary Ophthalmologists*, Chicago, 1983). In Sweden such a defect has also been observed and further studied in a complete litter of Briard dogs and in their parents. This paper

describes some of the clinical characteristics of the disease in these dogs and compares the results with the findings in cases of CSNB in man.

Subjects and methods

DOGS

A litter of nine 10-month-old Briard dogs and their parents were studied at the Faculty of Veterinary Medicine, Swedish University of Agricultural Sciences, Uppsala. Apart from apparent night blindness in some of the dogs the breeder claimed that her dogs had been healthy since birth. The affected dogs seemed to require rather bright light to see properly. The visual problems appeared to have been stationary from birth. A general clinical examination of the dogs did not reveal any signs of disease except for visual disturbances. The ophthalmic examination included examination of the direct and indirect pupillary light reflexes, an obstacle course test under dim and bright illumination, indirect ophthalmoscopy, and slit-lamp examination after the induction of mydriasis. Electroretinography (ERG) was performed finally in eight of the dogs.

To record the ERGs the animals were anaesthetised with intravenous sodium thiopentone, intubated, and maintained in surgical anaesthesia with halothane. The pupils were fully dilated by topical application of 0.5% atropine and 10% phenylephrine hydrochloride. A corneal contact lens electrode with a diffusing surface to provide even

Table 1 Clinical findings in 11 Briard dogs examined: five cases of nyctalopia

	Number/age/sex										
	1/10/F mo	2/10/M mo	3/10/F mo	4/10/M mo	5/10/F mo	6/10/F mo	7/10/M mo	8/10/F mo	9/10/M mo	10/7-5/F yr	11/6/M yr
Pupillary light reflexes	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Obstacle course test:											
dim light	Abnormal	Abnormal	Abnormal	Abnormal	Abnormal	Normal	Normal	Normal	Normal	Normal	Normal
bright light	Normal	Normal	Normal	Slightly abnormal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Ocular structures (external structure and anterior segment)	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Fundus	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Dark adaptation during ERG	Abnormal	Abnormal	Not done	Abnormal	Abnormal	Normal	Normal	Not done	Not done	Normal	Normal
Dark-adapted ERG	Barely recordable a and b waves	Barely recordable a and b waves	Not done	Barely recordable a and b waves	Barely recordable a and b waves	Normal	Normal	Not done	Not done	Normal	Normal
30 Hz flicker ERG	Subnormal	Subnormal	Not done	Subnormal	Subnormal	Normal	Normal	Not done	Not done	Normal	Normal

illumination of the retina was used. A reference needle was placed subcutaneously on the side of the nose near the tested eye and the dog electrically earthed through a needle at the occiput. A Tektronix amplifier (TM504) followed by a 0.3 to 1 kHz bandpass filter, a dual trace amplifier (5A18N), and a dual beam storage oscilloscope (5113) were used. Tracings on the oscilloscope were photographed with a Polaroid camera.

The light stimulus was provided by a 250 W halogen lamp and regulated by an electronic shutter (Uniblitz). Both a stimulating and a background light path were used and led to the eye via fibre optics ending 5 mm in front of the eye on the visual axis. Neutral density filters attenuated the 20 ms light stimulus in a 5 log-unit intensity range with 31 000 lux as the maximum light used.

The animals were dark-adapted for 30 minutes, during which time the dark adaptation was studied by stimulating the eye every 5 minutes with white light (31 000 lux). To study the sensitivity of the rod system a 20 μ V criterion response to white light was used for threshold determination, after a total dark adaptation time for 45 minutes. From a starting point of -5 log relative units the light intensity was increased in steps of 0.5 log units up to full intensity. To study the cone system the eye was light-adapted (50 lux) for 10 minutes and the responses to 30 Hz flicker with maximum luminance were studied. The a wave was measured from the baseline and the b wave from the trough of the a wave.

To compare directly the results from human ERG recordings one clinically affected litter mate and a normal 1-year-old beagle were studied under general anaesthesia (halothane) at the Department of Ophthalmology, University of Linköping, with a set-up similar to the one described below for clinical work on patients.

PATIENTS

Four patients between the ages of 6 and 12 years, with a history of nyctalopia, were examined and their condition diagnosed as CSNB at the Department of Ophthalmology, University Hospital of Linköping, Sweden. Clinical testing included tests of visual acuity, fundus examination, Goldmann perimetry, and tests of colour vision (Ishihara and Dvorine pseudoisochromatic plates) and dark adaptometry (Goldmann-Weekers).

The ERG recordings were performed under topical anaesthesia in case 4; the other three children required general (halothane) anaesthesia. The pupils were dilated maximally and a contact lens with a silver-silver chloride electrode was used. The reference electrode was attached to the forehead. The signals passed via the electrodes to a DC

amplifier and were then processed in a Hewlett-Packard computer system (HP 9826). Stimulus light, produced by a 150 W halogen lamp (Osram), passed heat absorbing and neutral density filters (Balzer) and an electromagnetic shutter (Uniblitz), and was then led by fibre optics to a tennis ball sized hemisphere, thus creating a single eye ganzfeld stimulus. The flash duration was 40 ms. The maximum intensity of the system, zero log unit intensity, was 18 000 cd/m², measured at the corneal surface. After 30 minutes of dark adaptation the eyes were exposed to light stimuli at an intensity level of -6, -4, -3, -2, and -1 log relative units. Four responses at each level were averaged. Photopic flicker ERG was recorded with a 30 Hz, -2 log unit, stimulus and 20 responses were averaged. For electrooculography (EOG) silver-silver chloride ECG electrodes were affixed near the nasal and temporal canthi of each eye. The patients alternately fixated two LEDs positioned in a sphere, separated horizontally by an angle of 60°. Recordings were made at 1-minute intervals during a 12-minute dark period, followed by a 12-minute light adaptation period. The results were printed out by the HP computer system. The Arden ratio was estimated.

Results

DOGS

Table 1 summarises the findings in the 11 Briard dogs studied. Pupillary light reflexes were normal in all dogs examined. Behavioural testing of visual function clearly differentiated affected animals from normal animals. In five of the nine litter-mates visual problems were observed in the dimly lit room; affected dogs tried to find their way round an obstacle course mainly by nose and frequently colliding with objects in their way. In two of the five cases the dogs were reluctant even to move around. When bright light was turned on none of them showed any major visual problems. Four of the affected dogs looked up and found their way around by using their eyes in a normal way, while one of them still moved in a somewhat hesitant manner. An examination of the eyes, including ophthalmoscopy and biomicroscopy, failed to show any abnormalities in any of the animals examined (Fig. 1).

Fig. 2a shows the ERG of a normal Briard dog. The ERGs of the affected Briards differed markedly from those of normal dogs. It was found that the three litter mates in which ERG recordings were performed at the Faculty of Veterinary Medicine and which had showed visual disabilities in the obstacle course test also had abnormal ERGs. There was no response at all when the stimulus light was attenuated, which means that there was no response at

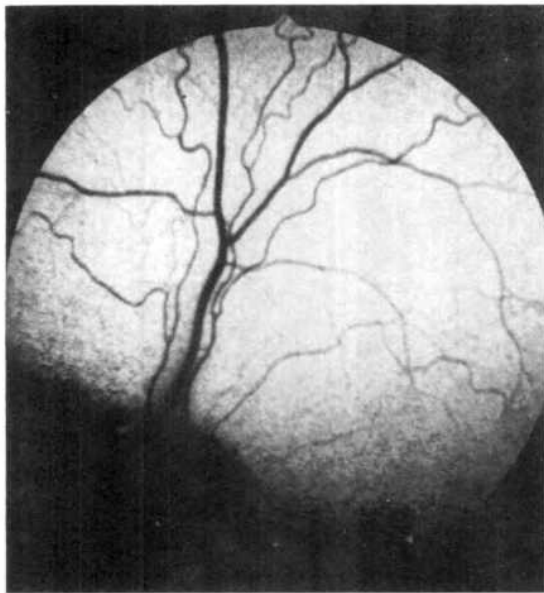


Fig. 1 The normal fundus appearance of a 10-month-old nyctalopic Briard dog (case 1).

scotopic levels. With the full light intensity, a 20 μ V criterion response was barely obtained (Fig. 2c). The full light intensity is clearly within the photopic range, and thus the only response obtained seems to be a reduced cone response. Photopic flicker responses from the affected animals were recordable (Fig. 2d), though subnormal when compared with the unaffected Briard dogs (Fig. 2b). This was further demonstrated at the University Hospital of Linköping, by means of the averaging technique, for one of the affected Briard dogs and a control (Fig. 3).

It is not possible to determine with certainty the genetic transmission of the defect when studying only one litter of affected dogs. The fact that both parents were unaffected, however, precludes a dominant inheritance of the defect. Both males and females were affected in the litter, which seems to rule out a sex linked inheritance. Thus the disease appears to be inherited in an autosomal recessive manner. We were surprised to learn from the study of pedigrees of the litter in Sweden and of affected Briards in the USA (Aguirre G, personal communication, 1988) that affected dogs from the two countries had common ancestors. As to how stationary these symptoms were, one of the nyctalopic dogs was donated for study and followed up for 1.5 years without any noticeable change in visual problems.

PATIENTS

Table 2 summarises the findings in patients with

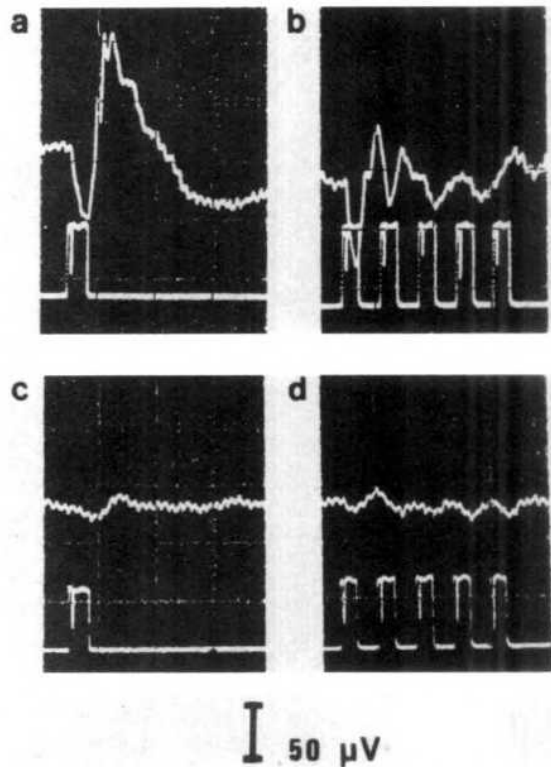


Fig. 2 (a) The normal dark-adapted ERG and (b) 30 Hz flicker response from an unaffected litter mate (case 7). (c) A dark-adapted, low-amplitude ERG and (d) subnormal 30 Hz flicker response from a nyctalopic dog (case 1). Dark adaptation time for (a) and (c) 45 minutes. 20 ms of white light stimulus (31 000 lux) is indicated below recordings.

CSNB. The visual fields were normal in all of them, as was the fundus appearance (Fig. 4). Colour vision was normal in two patients, slightly abnormal in one, and abnormal in one, though in the last case (case 1) the abnormality may have been due to unsatisfactory co-operation. A dark adaptation curve was not obtained in the two youngest patients, but there was a history of problems with night vision in both. In the other two patients a monophasic dark adaptation curve was recorded, in which only the cone branch was observed. A reduced light peak was recorded in the EOG in three out of the four cases.

In all four cases the dark-adapted ERG was abnormal (Fig. 5). In two cases the a wave had a normal amplitude, but it was slightly reduced in the other two. The b wave, on the other hand, did not exceed the baseline in any of the cases. Thus 'negative type' ERGs were found in all patients. In two of them a negativity following the b wave was also found. Cone responses (30 Hz flicker) were

Table 2 Clinical findings in four cases of human CSNB

	Number/age/sex			
	1/6/M yr	2/6/F yr	3/11/M yr	4/12/M yr
Corrected visual acuity	R: 1.0 L: 1.0	R: 0.4 L: 0.4	R: 0.8 L: 0.7	R: 0.6 L: 0.7
Refraction	R: +2.5 sph L: 0.6 +2.5	R: +3.5 sph L: +3.5	R: +1.0 sph -1 cyl 30° L: +1.5 sph -1.5 cyl 150°	R: -2 sph -3 cyl 90° L: -3.5 sph -1.5 cyl 90°
Visual fields	Normal	Normal	Normal	Normal
Fundus	Normal	Normal	Normal	Inferonasal fundus ectasia, otherwise normal
Colour vision	Abnormal	Mildly abnormal	Normal	Normal
Dark adaptation	DA curve not obtained (history of decreased DA)	DA curve not obtained (history of decreased DA)	Monophasic curve without rod adaptation	Monophasic curve without rod adaptation
EOG	Abnormal light peak	Abnormal light peak	Abnormal light peak	Normal
Dark-adapted ERG	a Wave slightly subnormal, b wave not exceeding baseline. 'Negative type'	a Wave slightly subnormal, b wave not exceeding baseline. 'Negative type'	a Wave normal, b wave not exceeding baseline. 'Negative type'	a Wave normal, b wave not exceeding baseline. 'Negative type'
30 Hz flicker ERG	Subnormal amplitude	Subnormal amplitude	Non-recordable	Subnormal amplitude

recordable in three of the four patients, but were somewhat subnormal in all three. No 30 Hz flicker response was obtained in the 11-year-old patient.

The four patients in this study were all referred from other parts of Sweden. Therefore it was not possible to determine with certainty the mode of inheritance for all of them. For case 2 the inheritance

was autosomal recessive and for case 4 X-linked. For cases 1 and 3 the inheritance was probably autosomal recessive.

Discussion

The patients with CSNB and the nyctalopic Briard dogs were similar in many respects. Firstly, the problems were congenital in nature. Affected dogs had shown strange behaviour and appeared unwilling to move around in new surroundings in dim lighting, at least after they were sold at the age of 7 weeks. The patients had always had visual difficulties, especially at night.

The stationary nature of the defect in the human disease, as well as its hereditary characteristics, have been well documented.¹⁻⁴ Since the four patients

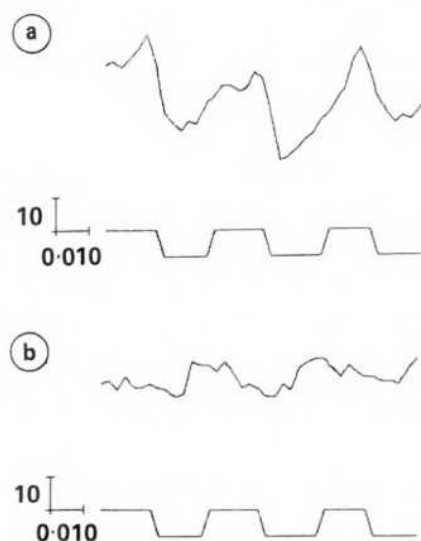


Fig. 3 The results from 30 Hz flicker recordings in which 20 responses were averaged. (a) The normal flicker response from a control dog. (b) The subnormal response from a nyctalopic Briard dog (case 4). Amplitude and time calibrations 10 μ V and 10 ms, respectively. Stimulus intensity -0.5 log relative unit (attenuation from a full intensity of 18000 cd/m^2).

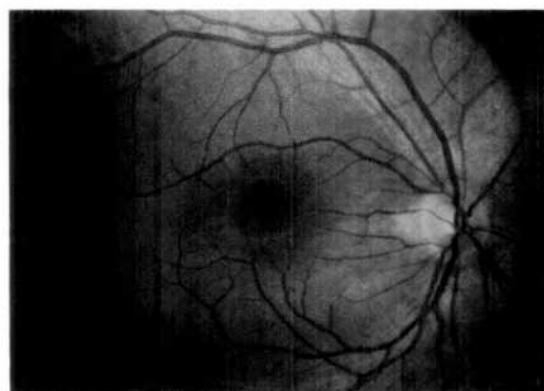
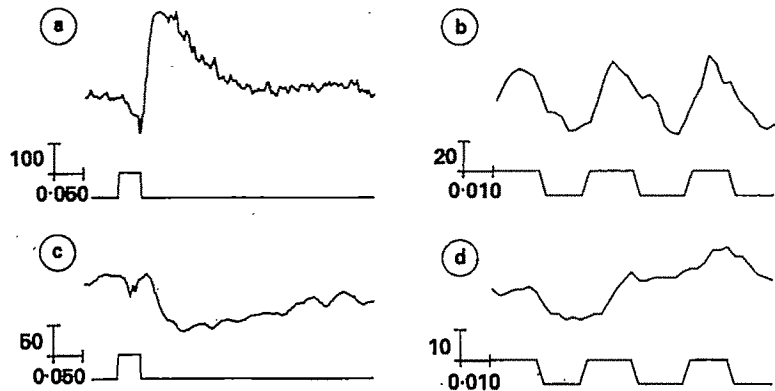


Fig. 4 Normal fundus appearance in the 11-year-old male (case 4).

Fig. 5 (a) The normal human dark-adapted ERG, and (b) 30 Hz flicker response. (c) A 'negative type' dark-adapted ERG (subnormal a wave and a low-amplitude b wave), and (d) subnormal 30 Hz flicker response from a CSNB affected patient (no. 1). Amplitude and time calibrations in μV and seconds. Stimulus intensity (a) and (c) -1 log relative units; (b) and (d) -2 log relative units.



described in this study were all referred from elsewhere and each was seen only once at the University Hospital of Linköping, there was no follow-up. There was no history of progressive disease in these cases, however. As regards the dogs, the owner was of the opinion that their visual symptoms had been stationary.

Several other similarities between the human and canine diseases were also found. In both types the affected individuals had normal fundi but were clinically night blind. The latter finding was verified through the monophasic dark adaptation curves found in two of the patients with CSNB and through the fact that scotopic ERG responses were lacking in the night blind Briards. Other forms of night blindness (retinitis pigmentosa, fundus albugineus, Oguchi's disease) were excluded because the disease was stationary and lacking ophthalmoscopically visible fundal changes.

A 'negative type' (type 1) ERG was found in the four patients, whereas the nyctalopic Briards showed a very low amplitude ERG, and at a photopic level only. When an ERG is very low in amplitude, it may be difficult to decide whether it is a type 1 or a type 2 ERG. However, the small a wave in our dogs may indicate that it is a type 2 ERG. We are aware of the depressant effects of halothane anaesthesia on the ERG.^{19,20} However, all dogs were tested by the same procedures, and therefore the results of affected animals and controls can be compared. As noted above, there does not seem to be any positive relationship between the type of ERG and the mode of inheritance. Thus it is not possible to decide whether the Briard disease correlates best with the autosomal recessive, the X-linked, or the dominant form of human disease. The 30 Hz flicker response was reduced in the human cases as well as in the affected dogs, which indicates that the photopic function is also impaired.

The major difference found so far between our four human cases and the affected Briards is in the single-flash ERG response. CSNB is an uncommon disease in Sweden, and the four cases we describe are the only ones we have seen in our hospital during the last five years. They all belong to the most common ERG type, type 1. Human cases of CSNB which show photopic (cone) ERG responses only, as in the Briard dogs, are rare.⁶ It could be argued that in such a form of the disease the rods are lacking rhodopsin, or bleached rhodopsin does not regenerate. However, as mentioned above, Carr *et al.*¹² described a case of human CSNB where only a small photopic response could be elicited, and in that case the concentration of rhodopsin, as well as the regeneration of rhodopsin after bleaching, was normal. This seems to indicate that at least the initial step of photochemistry is normal, whereas later events in the transduction mechanism are disturbed.¹²⁻¹⁴ It thus appears that the Briard dog, regardless of type of ERG response and type of inheritance, may become a valuable new animal model of human CSNB. Studies to determine further the hereditary, electrophysiological, and morphological characteristics in the canine model are in progress in relation to very young as well as older dogs.

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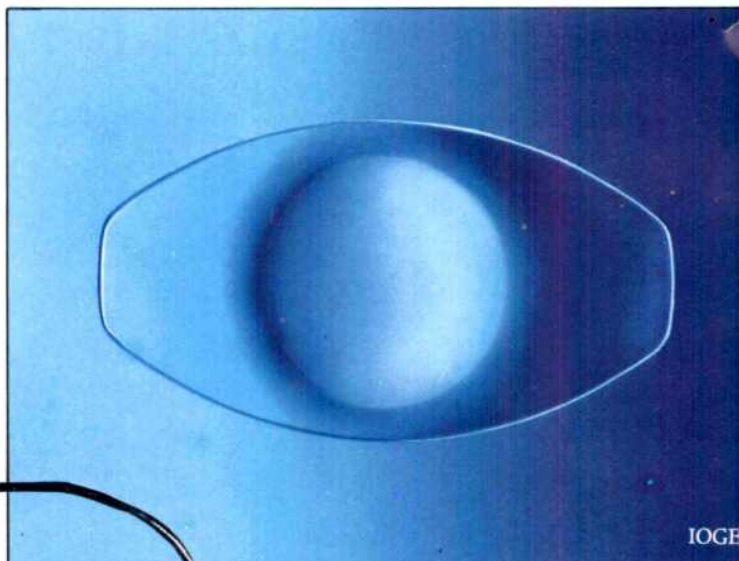
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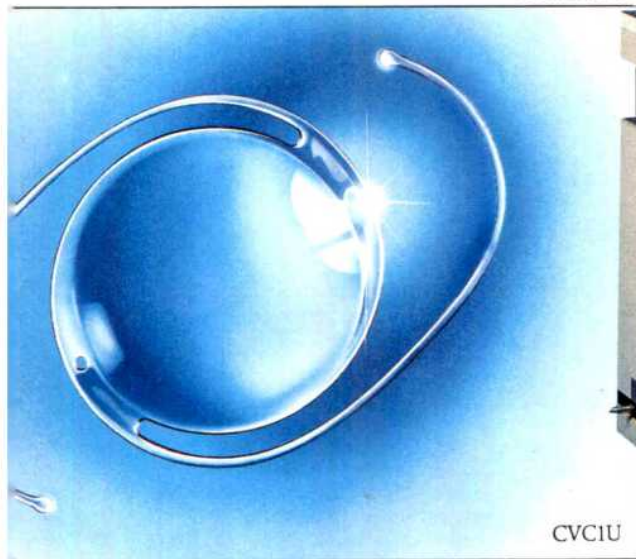


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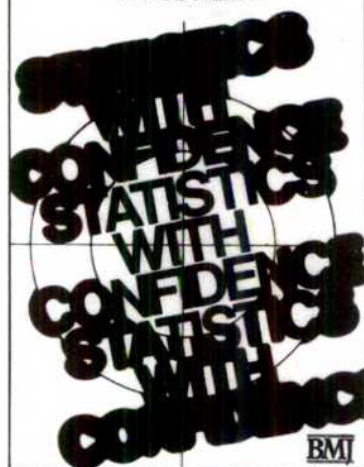
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A fibrin sealant for perforated and preperforated corneal ulcers

FRANÇOISE M LAGOUTTE, LAURENT GAUTHIER,
AND PASCAL R M COMTE

From the Department of Ophthalmology, Hôpital des Enfants, Bordeaux, France

SUMMARY Fibrin sealant is used to close perforated or preperforated corneal ulcers. In addition to the usual advantages of cyanoacrylates it is degraded physiologically and provides a good support for corneal healing. Corneal grafting can be avoided when contraindicated or postponed when conditions allow. This technique has been successful in nine eyes of eight patients.

Perforated corneal ulcers are difficult to treat, whatever their cause. The most commonly used treatment is emergency penetrating keratoplasty, but the poor visual prognosis for these emergency grafts requires other therapeutic solutions. The highly hydrophilic therapeutic lens can be used only for perforations of very small diameter.

The deposit of a layer of fibrin on the surface of the ulcer causes the anterior chamber to be closed immediately, with the hope that the cornea will subsequently heal. This avoids the need for grafts, which may fail if performed under unfavourable conditions, such as sicca syndrome or pemphigoid disease.

Materials and methods

The tissue adhesive used is Tisseel (Immuno France). Its action is the result of the interaction of two solutions. The first is an adhesive solution containing: (1) human fibrinogen freeze-dried at 30 times plasma concentration (90% proteins); (2) factor XIII, a fibrin-stabilising factor extracted from human plasma at 10 times plasma concentration (10 U/ml); (3) fibronectin (5% proteins); (4) low concentration plasminogen (0.13 g/l); (5) albumin (3% proteins); (6) aprotinin, a protease inhibitor of bovine origin at a concentration of 3000 UK. The second is a catalyst formed from a mixture of two solutions: (1) freeze-dried thrombin at two different concentrations, namely, 500 U-NIH/ml for rapid setting in 30 seconds,

and 4 U-NIH/ml for slow setting in 3 minutes; (2) calcium chloride at a concentration of 40 mmol/l.

A surgical microscope and a local anaesthesia with oxybuprocaine drops are used, and the eye is opened with a blepharostat. The abrasion of necrotic tissue is performed with cellulose sponges.

Thrombin is used at a 500-U-NIH/ml concentration to ensure rapid setting. The two previously prepared solutions are applied either simultaneously via a single mixing needle (a technique possible thanks to the Duplojet device delivered with the kit) or successively, when the fibrin solution should be applied first, as it is more viscous and less likely to run. We ourselves prefer simultaneous application, as it provides both more homogeneous polymerisation and the optimal concentration ratio for the different compounds.

After two minutes' setting the tissue adhesive will have extended considerably beyond the edges of the ulcer and the excess must be cut to a smooth bevel. This is an easy task, as the tissue adhesive has very little adherence to the epithelium of the healthy cornea, where there is no collagen, the substance with which fibrin crosslinks.

A soft lens is applied in order to limit any shearing forces due to palpebral movements which could remove the sealant plug.

A flat anterior chamber can be deepened by a viscous substance such as sodium hyaluronate prior to the use of the tissue adhesive if the anterior chamber is still watertight enough to retain the viscous substance, or subsequently if not. In the latter case any iridocorneal synechiae should be reduced via the limbic injection punctum.

Postoperative treatment consists of four daily instillations of antibiotic drops. The durability of the tissue adhesive is considerably increased by six daily instillations of aprolin (Iniprol), as in cases 6, 7, 8, and 9.

Results

Presented chronologically, these demonstrate the successful evolution of the technique.

CASE 1

A 61-year-old female, with severe pemphigoid disease. The right eye was already lost owing to a corneal perforation with unsuccessful keratoprosthesis. In the left eye there was ulcerative vascularised keratitis. During an attack of increased inflammatory cornea this developed a perforated ulcer and overall thinning. After application of fibrin sealant the ulcer closed over and remained so for 18 months, thus leaving a corneal leucoma and enabling the patient to maintain her poor vision as before.

CASE 2

A 74-year-old woman with inferior paracentral perforated ulcer in a very serious keratoconjunctivitis sicca. The patient presented with a totally collapsed anterior chamber, which was reformed within 48 hours by means of a bandage contact lens; the ulcer opened again afterwards. Fibrin sealant was then applied together with reformation of the anterior chamber with sodium hyaluronate introduced by a limbic puncture. The sealant plug was lysed within 48 hours, but the ulcer was definitively blocked off. Ten months later, there was still a corneal leucoma at the site of the perforation, the anterior chamber was quiet with no iridocorneal synechiae, and visual acuity was 20/80. No keratoplasty was programmed because of the sicca syndrome.

CASE 3

A woman aged 61 who had a graft in 1982 for an herpetic corneal necrosis. A further necrotic ulceration of the graft occurred in December 1985. She was admitted to hospital on 27 December 1985 for perforation of the ulcer. No emergency transplant was available, so the ulcer was filled with Tisseel and the anterior chamber was deepened. Here again the Tisseel was covered with a bandage contact lens. Her condition remained stable for three days, after which the ulcer opened again. However, it was then possible to make a transplant. In this case though the sealant did not ensure sufficient closure to avoid a transplant, it made it possible to wait for a graft under satisfactory conditions (closure of the fistula, reformation of the anterior chamber).

CASE 4

This man aged 66 had had a right torpid corneal ulcer of traumatic origin six months previously. He was admitted to hospital initially for keratoplasty. Examination revealed an unperforated descemetocoele and a satisfactorily quiet anterior chamber. Tissue adhesive was applied together with a bandage contact lens. Twelve days later the sealant was still in place and the ulcer had healed; a transplant was performed four months later. After two years the visual acuity was 20/30.

CASE 5

A man 81 years old with chronic paracentral inferior ulcer of the left eye of unknown origin. The ulcer was developing into a descemetocoele. A layer of fibrin sealant was applied, together with a bandage contact lens. The ulcer healed with a visual acuity of 20/30, but the patient was lost to follow-up. He returned four months later with bilateral purulent conjunctivitis and left corneal necrosis too severe for any treatment by this method. In fact the origin of the ulcer proved to be a chronic dacryocystitis.

CASE 6

A 51-year-old woman with Sjögren's syndrome, who had received no ophthalmic care. She had perfectly symmetrical perforations of both corneas, and stated she had had them for three weeks. Both perforations were round, with a punch diameter of 2.5 mm, paracentral and temporal, with an iris plug in the ulcer, positive Seidel's test, and a collapsed anterior chamber (Fig. 1). The fibrin sealant was applied at the site of perforation, and the anterior chamber was deepened by limbic puncture after sealing, since the viscous substance would not have remained in the anterior chamber. Seventy-two hours later the sealant plugs had completely dissolved, making it necessary



Fig. 1 Case 6, left eye, perforated ulcer with positive Seidel's test and iris plug prior to treatment.



Fig. 2 Case 6, with sealant plug and bandage lens three days after treatment.

to reapply the sealant. A bandage lens was applied. To avoid rapid fibrinolysis, aprotinin was instilled six times a day. The sealant remained one month (Fig. 2), leaving a bilateral corneal leucoma. The anterior chamber was quiet. In both eyes there was a very slight filiform iridocorneal synechia at the perforation site; this would have been insufficient to close a perforation of that size. Two months later the corrected visual acuity was 20/30 right eye, 20/25 left eye, with an ocular pressure of 10 mmHg in both eyes; the scar was stable and no graft was advised (Fig. 3).

Four months later the visual acuity was 20/60 right eye, 20/25 left eye. New stromal inflammation had appeared in previously healthy areas but was stopped with the usual medication.

CASE 7

A 66-year-old man, suffering from a rosacea presented with an ulcer of the right eye which had perforated 7 days previously. This perforation, which was a clear 2 mm hole, temporal paracentral, was



Fig. 3 Case 6, two months later with stable scar and 20/15 acuity.

blocked by an iris plug. Fibrin sealant was placed in the perforation and the anterior chamber was reformed with sodium hyaluronate introduced by limbic puncture. A bandage lens was applied and Iniprol was instilled 6 times a day. Complete healing ensued after one month. The visual acuity was 20/60 and a graft was not advised.

CASE 8

A 13½-year-old child was suffering from corneal anaesthesia and facial paresis owing to a lesion of the posterior fossa. An ulcer, which had started a month earlier, had perforated. The lens was blocking the perforation. Fibrin sealant was applied, and the anterior chamber was reformed with sodium hyaluronate. A partial tarsorrhaphy was also performed, and Iniprol was instilled six times a day. After two months the ulcer seemed to be definitely healed.

Discussion

The idea of using surgical glue in the treatment of perforated or preperforated ulcers is not new. As early as the 1960s surgical sealants and their various applications were proposed.^{1,2} A study of cyanoacrylates revealed that their properties depend on the chemical variety used. These sealants are known to have anti-infectious properties inversely proportional to the length of their constituent monomers³ and an inhibiting effect on corneal necrosis.⁴ Their ocular toxicity, however, is variously assessed. Some workers consider cyanoacrylates are responsible for corneal inflammation, neovascularisation of the stroma, and inflammatory reactions in the anterior chamber,^{5,6} while others consider that they are well tolerated.^{7,8}

In fact, tolerance to cyanoacrylate varies according to the quantity of glue. When very little is used, the inflammatory reaction and vascularisation are minimal, but when the glued area covers as much as a quarter of the cornea the result is poor.⁹

For a long time the requirement not to introduce this glue into the anterior chamber meant that cyanoacrylates were used for small diameter (1 mm) perforations. (An air bubble placed inside the anterior chamber stopped any glue from entering.) Hirst and De Juan¹⁰ were the first to combine the use of sodium hyaluronate and cyanoacrylates to treat perforations up to 3 mm. The use of a free tissue patch associated with cyanoacrylate made it possible to limit this penetration even more.¹¹

Perforations and descemetocles treated with tissue adhesive have a better prognosis, as shown by Hirst and associates,¹² who report an improvement in visual acuity in eyes treated with this technique and a clear decrease in the enucleation rate (6%). This has

been confirmed by Weiss *et al.*¹³ Similarly Foster and Duncan¹⁴ have obtained a much better prognosis for grafts performed after cyanoacrylates have been used (85% clear grafts) than those practised 'à chaud' (no clear grafts).

Such perforations can also be treated by lamellar graft. The corneal lamella may come from a fresh donor eye; in this case the quality of the donor cornea is not important. A lamella graft may also be sealed by fibrin sealant, and Flacinelli *et al.*¹⁵ report on four patients, two of whom recovered visual acuity of 80/60 and 20/100. With this procedure a third patient was able to wait for a perforating graft.

More recently a planolyophilised epikeratopatch stitched to the surface of the perforated cornea has been proposed for the same purpose (McDonald M B, Kaufman H E, Koenig S B, personal communication). This technique has the advantage of being available for treating perforations of more than 2 mm diameter but is very expensive and perishable.

The use of a fibrin sealant has many advantages. It is justified by the high collagen content of the corneal stroma denuded by the ulceration. Duckert *et al.*¹⁶ and Mosher¹⁷ have demonstrated the crosslinking of fibrin and fibronectin with collagen. This crosslinking explains the high adherence of this sealant to collagen-rich tissue. It stimulates healing owing to the presence of factor XIII in the fibrin sealant; these substances are known to stimulate the proliferation of fibroblasts.¹⁸ It has some anti-infectious activity: Stanek *et al.*¹⁹ have shown that a strain of *Staphylococcus aureus* grows less in a fibrin clot than in a blood clot. It has no corneal toxicity²⁰ and no toxicity for the lens. On the contrary, Buschmann *et al.*²¹ have shown that fibrin can be used to stop a perforation of the anterior capsule of the lens in order to avoid opacification.

A fibrin sealant has already been used experimentally in the rabbit to repair retinal tears.²² Pathological examination revealed perfect tolerance and in particular no tendency to promote vitreoretinal proliferation.

The use of a substance of human origin raises the problem of virus transmission, particularly hepatitis B and HIV. In order to avoid such transmission the plasmas used are subjected to radioimmunoassay (Hbs), and enzyme linked immunosorbent assay (ELISA) for anti HIV antibodies, in accordance with the criteria accepted by the F.D.A. The same tests are repeated on the plasma pools formed after fractionation and on the Tisseel itself. After freeze-drying the finished product also undergoes thermoviroinactivation for 30 hours at 60°C. This method has been used experimentally to inactivate high concentrations of three model viruses (Sinobis virus, vesicular stomatitis virus, and HTLV III.

It has also been proved that the use of fibrin seal does not increase the risk of non-A non-B hepatitis.²³

In our experience, this simple technique has made it possible to avoid keratoplasty in nine patients, for four of whom a severe sicca syndrome meant a very poor prognosis for any graft, even after the perforation had completely healed. We have never encountered any problems with infection of the treated ulcer, nor has any residual inflammation of the anterior chamber been observed after resorption of the inflammatory reaction due to the perforation.

The technique is simple, non-invasive, and fully reversible. It has the major advantage over synthetic sealants of providing a true support and helping the cornea to heal. The clot of fibrin applied degrades very gradually and is replaced by fibrosis, of which it forms the initial web. In the event of failure it in no way hinders keratoplasty and can even improve the prognosis. When successful the perforation is replaced by a corneal scar which, if not on the visual axis, or if a graft is contraindicated, enables keratoplasty to be definitely avoided.

The use of this organic sealant has in addition to the usual advantages of surgical sealants those of being well tolerated, degraded by the physiological and non-inflammatory mechanism of fibrinolysis, and of providing a good support for corneal healing.

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Bilateral anterior ischaemic optic neuropathy associated with optic disc drusen and systemic hypotension

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SUMMARY We report a case of bilateral anterior ischaemic optic neuropathy in a 23-year-old woman which was probably attributable to optic disc drusen and systemic hypotension related to peritoneal dialysis for renal failure.

Non-arteritic anterior ischaemic optic neuropathy (AION)¹⁻³ appears to be the result of obstruction of axoplasmic flow owing to ischaemia, leading to a cascading effect via further small vessel compromise^{4,5} in the setting of underlying disc crowding.⁶⁻⁸ It has been reported in patients, some relatively young, with drusen of the optic nerve head.^{9,10} We report on a young woman with systemic hypotension who had optic disc drusen and developed bilateral AION while on home peritoneal dialysis.

Case report

A 23-year-old white female noticed on awakening the painless loss of inferotemporal vision in the left eye in late February 1986. On 14 March her visual acuity was 20/20 on the right and 20/25 +3, with marked relative afferent pupillary defect and marked constriction of visual field on the left. There were drusen of both optic discs, with swelling of the left. A CT scan of the head and orbits was considered normal.

On 22 May her visual acuity was 20/20 in each eye without relative afferent pupillary defect. The right disc pale and elevated, the left flat and mildly atrophic. In early June she awoke with marked diminution of vision in the right eye and was referred to our Neuro-ophthalmology Clinic on 20 June.

She had been on haemodialysis for chronic renal

failure following post-streptococcal glomerulonephritis until 1984 and on peritoneal dialysis thereafter. She was chronically hypotensive, with blood pressure 52/38 and 62/38 mm Hg at clinic visits in January and February 1986. An oral contraceptive (Ortho-Novum, norethisterone with ethinyloestradiol) taken for approximately four years was discontinued when visual symptoms first developed. Her visual acuity was finger counting at 2-3 feet (60-90 cm), with hand motion only superotemporally in the right eye, and 20/20 +3 with the field concentrically constricted on tangent screen in the left eye. Colour plates (AO-HRR): 0/6 OD, 6/6 OS.

External, motility, and slit-lamp examinations gave normal results. Tension by applanation was 16 in each eye. Her pupils were sluggish, with a marked right relative afferent defect. There were bilateral disc drusen, with right more than left optic atrophy, and diffuse thinning of the nerve fibre layer (Figs. 1 and 2). Calcification was evident in both optic nerve heads on review of her orbital CT scan (Fig. 3).

Discussion

Various factors may have contributed to apparent bilateral consecutive AION in our patient, with optic disc oedema preceding visual loss by weeks in the second eye, as may occur.^{2,11} She had optic disc drusen in both eyes, which have been associated with transient visual obscurations¹² and permanent visual loss,¹³ including AION.^{9,14} Preceding transient visual

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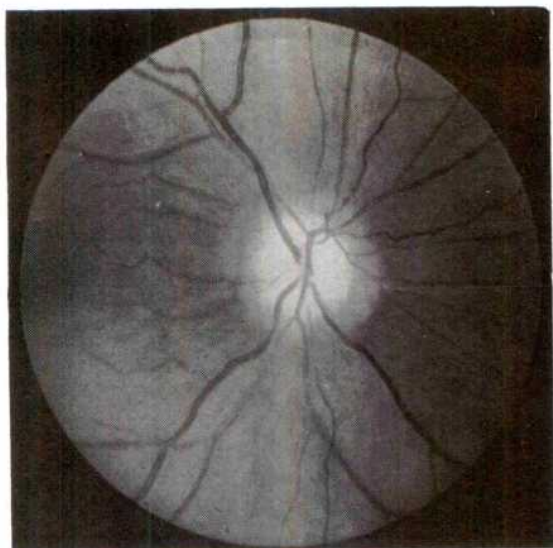


Fig. 1 Appearance of right optic disc on 20 June 1986.

loss⁹ and recurrent episodes of AION have been reported.¹⁵ Hypotension has been suggested, in addition to increase of intraocular pressure,¹⁶ as a basis for the frequent finding of visual loss in AION, as in our patient, on awakening. Impairment of autoregulation of optic nerve perfusion may have been an additional factor in our patient, who was chronically hypotensive. This was postulated by Taylor *et al.*¹⁷ in his cases of AION following sudden reduction in systemic blood pressure in chronically

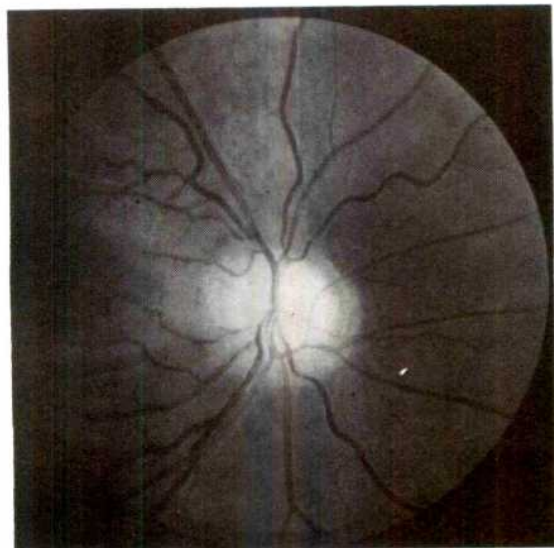


Fig. 2 Appearance of left optic disc on 20 June 1986.

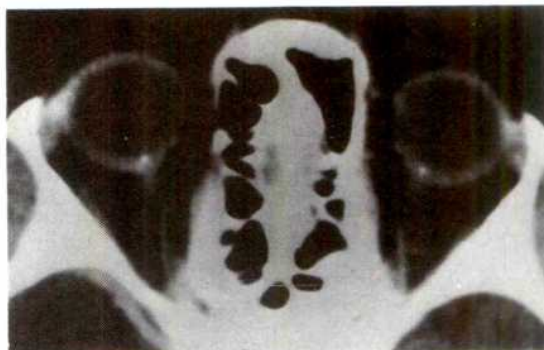


Fig. 3 Orbital CT scan in March 1986 showing bilateral optic nerve head calcification.

hypertensive children with disc swelling. Drusen, through mass effect, may have raised the intraneural tissue pressure,¹² leading to greater susceptibility to ischaemia. The crowded discs reported with drusen,^{15,18} as in our patient and others,⁹ may have been another factor. Increased circulating vasoconstricting agents may exacerbate hypoperfusion in the setting of hypotension in posthaemorrhagic AION¹⁹ and in AION following cardiopulmonary bypass.^{20,21} Peritoneal dialysis may have contributed to her AION, as suggested by the association with haemodialysis^{16,22} together with hypotension²² and intraocular pressure elevation^{23,24} in that setting. Oral contraceptives, reported to be associated with various forms of vaso-occlusive disease (including possibly AION²⁵) even months after their cessation, seem unlikely to be of significance in our patient, though not entirely excluded.

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Acute posterior multifocal placoid pigment epitheliopathy complicated by central retinal vein occlusion

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SUMMARY A case of acute posterior multifocal placoid pigment epitheliopathy (APMPPE) complicated by a central retinal vein occlusion five weeks after presentation is described. After eight months' follow-up there was mild residual visual impairment, macular scarring, and angiographic changes. The association of these two conditions is discussed.

Acute posterior multifocal placoid pigment epitheliopathy (APMPPE) was first described by Gass in 1968.¹ Since then there have been many clinical descriptions of the disease, but the aetiology remains elusive. A substantial proportion of cases have an associated viral-like prodromal illness, and one case of APMPPE associated with confirmed adenovirus type 5 infection has been reported.² Associations have also been made with systemic inflammatory conditions—erythema nodosum,^{3,4} sarcoid,⁵ thyroiditis,⁶ nephritis,⁷ and cerebral vasculitis.⁸⁻¹²

Case report

A 28-year-old woman presented to the eye casualty department with complaints of dull frontal headache of two days' duration and deterioration in central vision in her right eye for 24 hours. She was otherwise well and was not taking any medication. The only significant past history was an episode of parieto-frontal headache eight years previously; investigations at that time, including a CT brain scan, gave normal results.

Examination revealed visual acuities to be 6/36 right eye and 6/4 left eye unaided. The anterior segments appeared normal. The right fundus had cream coloured placoid lesions, $\frac{1}{2}$ to 1 disc diameter, scattered across the posterior pole mainly in the superior half (Fig. 1). The macula was notably oedematous. The left fundus was entirely normal.

A diagnosis of acute posterior multifocal placoid pigment epitheliopathy was made.

Intravenous fluorescein angiography showed early hypofluorescence and late hyperfluorescence of the lesions (Figs. 2, 3) typical of APMPPE. Full and differential blood cell count were normal. The erythrocyte sedimentation rate was 6 mm/h. Radiography of chest, cranial vault, pituitary fossa, orbits, and optic foraminae showed normal appearances. An enzyme linked immunosorbent assay (ELISA) for toxoplasma was negative. Acute and convalescent serum samples did not show a rising titre to adenovirus, measles, herpes simplex, varicella zoster, cytomegalovirus, or leptospira.

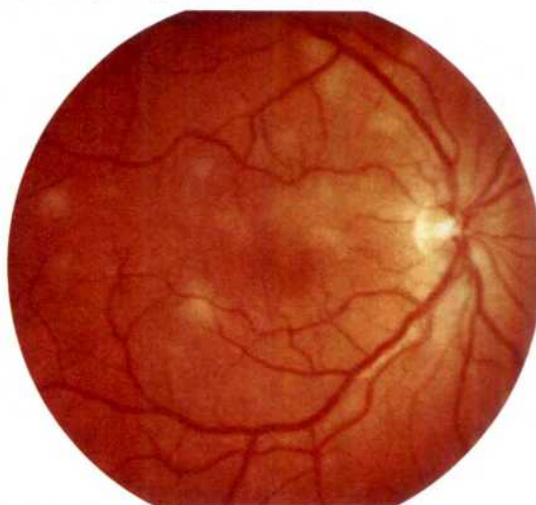


Fig. 1 Right fundus on initial presentation.

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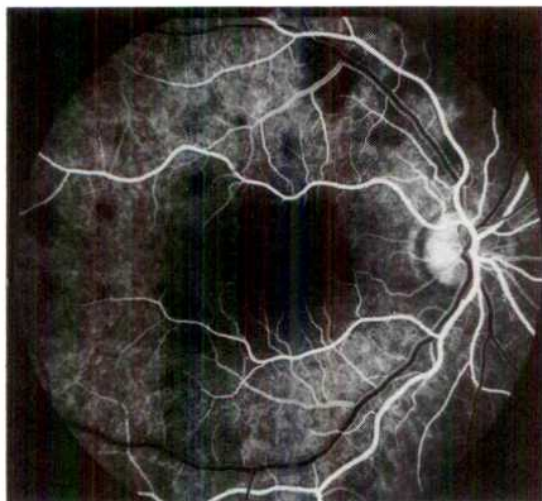


Fig. 2 Early venous phase fluorescein angiogram showing hypofluorescence of placoid lesions.

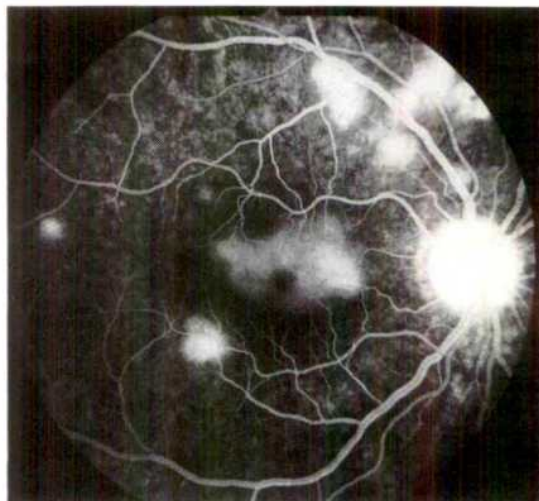


Fig. 3 Late phase fluorescein angiogram showing hyperfluorescence of placoid lesions and macular oedema.

In view of the macular oedema she was started on prednisolone 80 mg per day, which was slowly reduced over four weeks. During this period the placoid lesions were essentially unchanged. The macular oedema showed some resolution, with reactive pigmentary changes, and the visual acuity improved to 6/24.

When she was examined at the clinic five weeks after her initial presentation, her right fundus had the appearance of a central retinal vein occlusion (Fig. 4). The right optic disc was swollen, and there were

flame-shaped haemorrhages extending from the disc and scattered linear and blot haemorrhages in all four quadrants. The placoid lesions were now more widespread and were becoming confluent. There was a right relative afferent pupillary defect, and her vision was 6/36 in this eye. The left eye remained unaffected. Fluorescein angiography confirmed the central retinal vein occlusion and the widespread placoid lesions but showed no evidence of retinal vasculitis (Figs. 5, 6). The fundus was not ischaemic, and no treatment was undertaken. The fundal

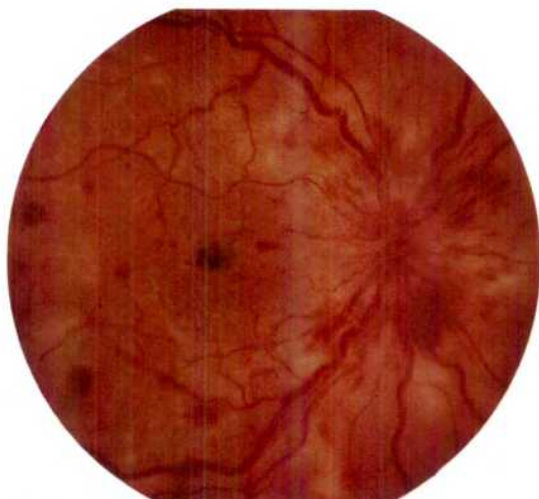


Fig. 4 Right fundus five weeks following initial presentation. A central retinal vein occlusion is superimposed on the placoid lesions.

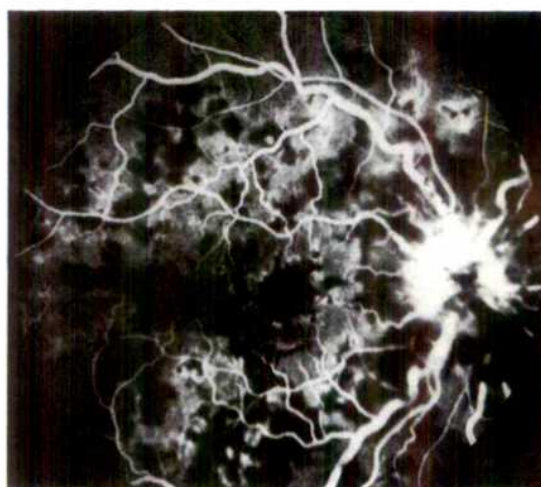


Fig. 5 Venous phase fluorescein angiogram demonstrating masking by retinal haemorrhages and areas of hypofluorescence due to the placoid lesions.



Fig. 6 Late phase angiogram. The placoid lesions now hyperfluoresce at their edges, though some lesions continue to hypofluoresce centrally.

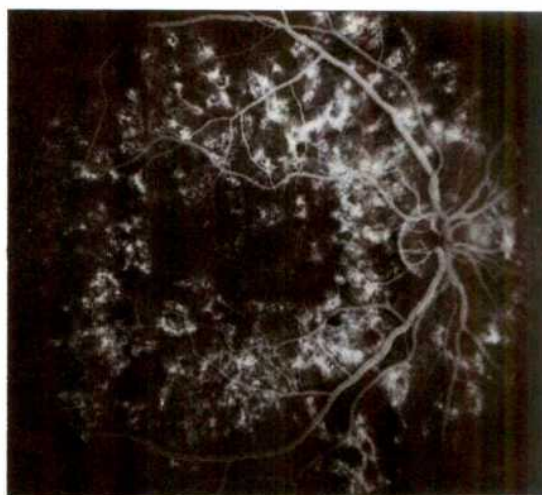


Fig. 7 Fluorescein angiogram eight months after presentation showing patches of hyperfluorescence throughout the posterior pole.

appearance slowly resolved, and the visual acuity improved to 6/9 after eight months' follow-up, when her only complaint was a small central scotoma. Fluorescein angiography at this stage showed patches of hyperfluorescence across the posterior pole (Fig. 7), and the macula had a residual pigmented scar (Fig. 8).

Discussion

The case described showed the typical early features of APMPE—loss of central vision with multiple cream coloured placoid lesions distributed over the posterior pole at the level of the retinal pigment epithelium. Uniocular cases are unusual but have been reported.^{13–16} The initial clinical impression of full visual recovery in APMPE¹ has been questioned in more recent work,^{13 14 17} and the residual impairment of central vision in this case is attributable to the macular involvement.

There have been no previous reports of central retinal vein occlusion occurring in APMPE. The observed changes in this case were typical of a central retinal vein occlusion¹⁸; there was only a minimal effect on vision and no evidence of fundal ischaemia or retinal vasculitis.

The primary site of the inflammatory process in APMPE is debated. Some authorities think that the retinal pigment epithelium is the primary focus,^{1 19 20} while others think that there is a choroidal vasculitis with secondary ischaemic changes in the retinal pigment epithelium due to occlusion of choroidal arterioles supplying individual choroidal

lobules.^{3 4 7 8 15 16 21–24} Many cases of central retinal vein occlusion in young people are thought to be due to inflammation within the vein¹⁸; optic disc vasculitis presents a similar fundal picture.²⁵ The occurrence of the two conditions together lends weight to the theory that APMPE is due to a choroidal vasculitis and is part of a more widespread systemic inflammatory process.^{3–12} The reported association of APMPE with retinal vasculitis and papillitis may be part of the same pathological process.²¹

It is perhaps surprising therefore that central

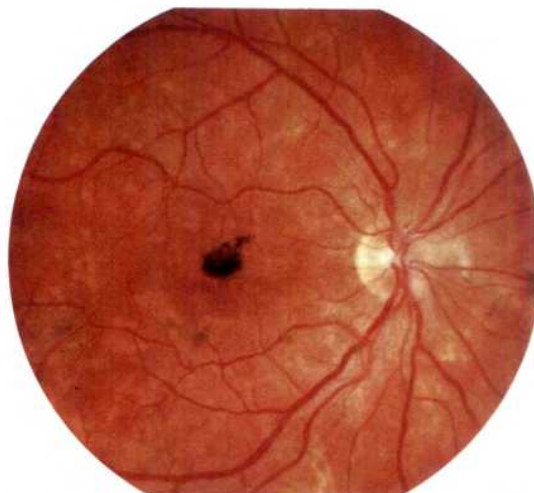


Fig. 8 Fundal appearance eight months after presentation. Note the pigmented macular scar.

retinal vein occlusion has not been previously reported in APMPE. The explanation of this may be that many cases of APMPE are asymptomatic unless there is macular involvement, and when it is complicated by venous occlusion the fundal features of APMPE are masked. In some cases the patchy hypofluorescence of the placoid lesions may be interpreted as capillary closure on fluorescein angiography.

The place of steroids in the treatment of APMPE is unproved. A recurrence following withdrawal of steroids has been reported.²⁶ In the case reported here it is notable that the venous occlusion occurred in the week following withdrawal of systemic steroid treatment. If vasculitis is implicated in the pathogenesis of the condition, steroid treatment may well have a role in the prevention of complications.

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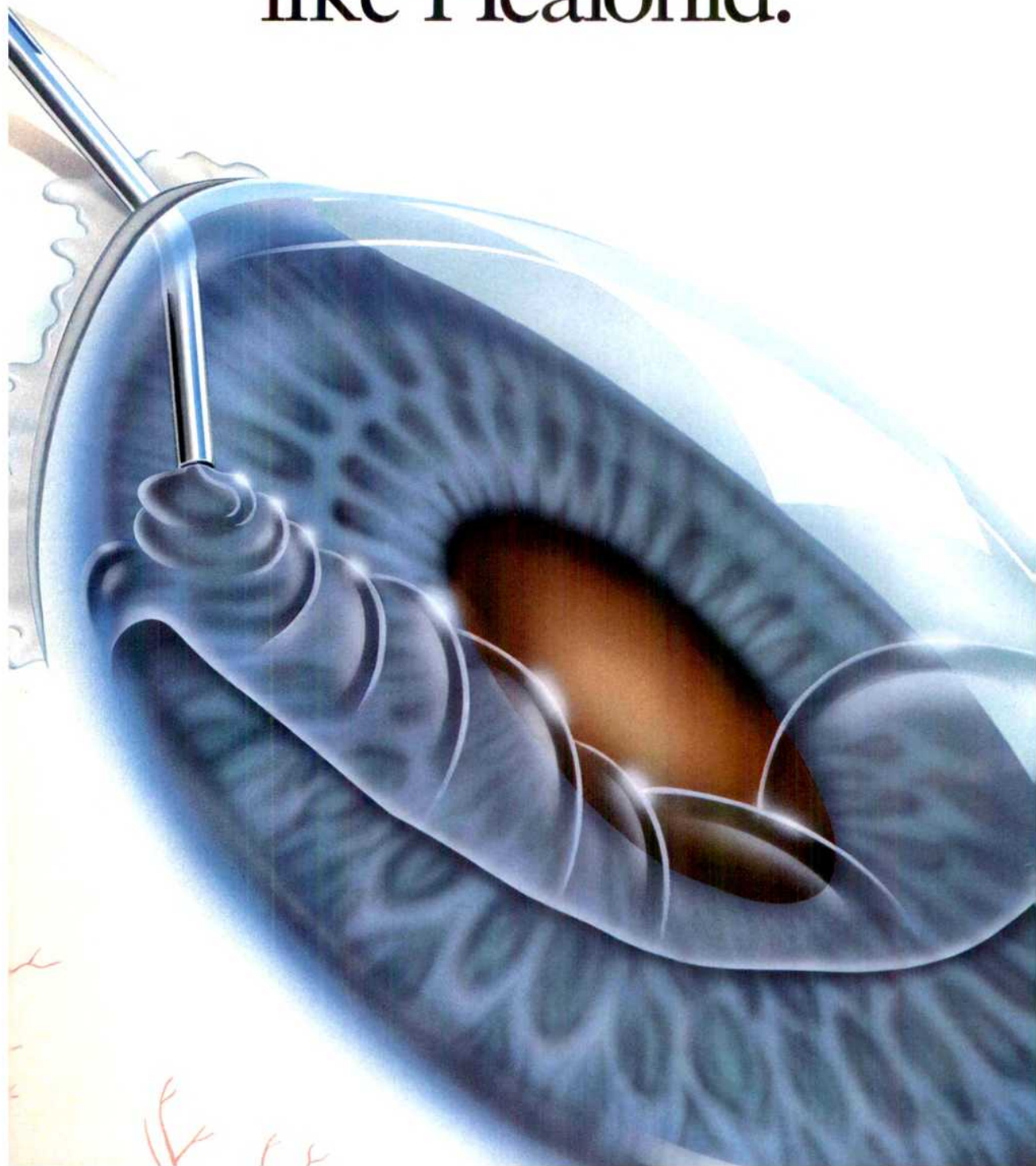
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Orbital cellulitis complicating isolated unilateral sphenoidal sinusitis: importance of the CT scan

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SUMMARY A case of orbital cellulitis complicating the rare isolated unilateral sphenoidal sinusitis is reported, stressing the importance of a CT scan where plain x-rays fail to show any abnormality.

Orbital cellulitis may result from different septic foci, sinusitis being a common source. Treatment must be directed towards the source of infection. Orbital cellulitis as a complication of isolated unilateral sphenoidal sinusitis is very rare. Underlying sinusitis in cases of orbital cellulitis is usually diagnosed with plain x-rays. However, plain x-rays may prove inadequate in cases of sphenoidal sinusitis, for they may fail to show the abnormality, so that correct treatment may be delayed. This risk can be avoided by promptly performing a CT scan.

Case report

A 71-year-old Caucasian woman presented with a sore, swollen, tender left eye of three days' duration. She was receiving treatment to both eyes for chronic simple glaucoma (timolol maleate and dipivefrin hydrochloride). For the previous six years she had received oral prednisolone 10 mg daily for rheumatoid arthritis. For three months she had been on rifampicin, isoniazid, and pyridoxine for pulmonary tuberculosis.

At presentation she was afebrile. There was massive left orbital swelling, with very injected conjunctivae and chemosis but no lymphadenopathy. The cornea was clear, and the intraocular pressure was raised at 34 mm Hg. The pupil was enlarged and reacted sluggishly to light. The retina showed no choroidal folds or other abnormality. There was no proptosis. Her visual acuity was 6/6 right eye and hand movements left eye (recorded 6/9 one month previously).

Plain x-rays of the paranasal sinuses (Fig. 1) were

reported by an experienced radiologist as normal. Treatment was begun with intravenous ampicillin and flucloxacillin (250 mg of each six hourly). Despite 24 hours of treatment there was increasing orbital swelling. A CT scan of the orbits and sinuses

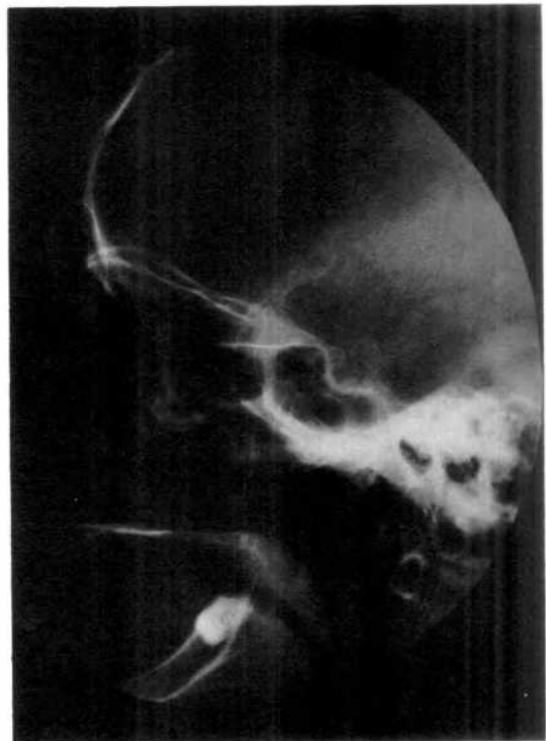


Fig. 1 Lateral x-ray. Sphenoidal sinuses of normal appearance.

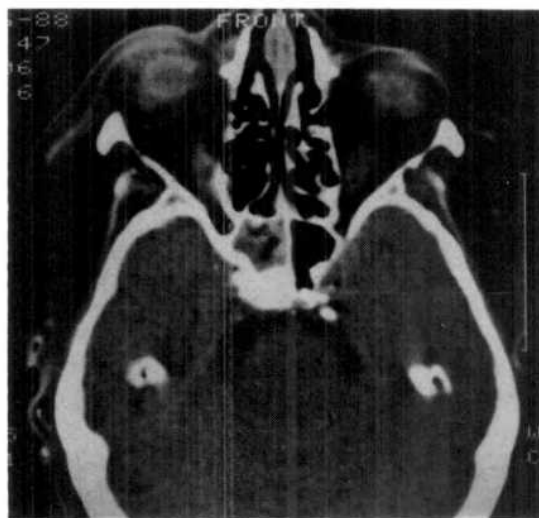


Fig. 2 Computerised axial tomography showing opacification of the left sphenoidal sinus.

was performed. This showed opacification of the left sphenoid sinus (Fig. 2). Her antibiotic dosage was therefore doubled and the opinion of an otolaryngologist sought.

The left sphenoid complex was approached through a Howarth incision. The anterior, middle, and posterior groups of ethmoidal cells were found to be healthy. The sphenoid sinus, however, was found to be lined by thickened mucosa and filled with inspissated mucus. All diseased mucosa was cleared, and the lateral wall of the middle meatus was widely excised to allow adequate drainage of the surgically created sphenoid cavity.

No organism could be isolated despite prolonged culture of samples of both mucosa and mucus. Histological examination of the mucosa revealed chronic inflammation. No granuloma or caseation was found.

After the operation the cellulitis resolved in 48 hours and vision improved to 6/18 (left eye) at two weeks, settling to 6/12 at four months.

Discussion

Since the days of Hippocrates sinusitis has been recognised as a common cause of orbital cellulitis.¹

The source of infection is usually the ethmoid, followed in frequency by the maxillary and frontal sinuses.¹ Though well recognised, isolated sphenoidal sinusitis is rarely the cause, and rarer still are reports of isolated unilateral sphenoidal sinusitis causing orbital cellulitis.^{1,2}

Dale and Mackenzie² reported on a series of five patients with complications of sphenoidal sinusitis in whom the diagnosis was easily made with plain x-rays. These should include the submento vertical and lateral views to demonstrate the sphenoid sinuses, so that the rare, but important, diagnosis of sphenoidal sinusitis is not missed.^{1,4} However, there is a 15% incidence of failure to detect sphenoidal sinusitis with plain x-rays.³ Plain x-rays may therefore allow the correct diagnosis to be made but cannot be relied upon to exclude underlying sphenoidal sinusitis, as found in our patient.

In orbital cellulitis CT scan is usually considered for patients who fail to respond to medical treatment.⁶ Early diagnosis and treatment are essential to minimise the risk of severe visual loss.⁷ Surgical intervention is required early in cases with underlying sinusitis to minimise this risk.⁸ Our dependence on plain x-rays delayed the diagnosis of the underlying pathology and hence necessary surgical intervention. Fortunately there was no serious visual loss. When no cause can be found on plain x-rays of the paranasal sinuses, CT scan can be useful in establishing the diagnosis and avoiding delay in giving the correct treatment.

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Accepted for publication 3 April 1989.

Correspondence

Ocular melanoma

SIR, Since the publication of the article by Bomanji *et al.*¹ on radioimmunoscintigraphy in the diagnosis of ocular melanoma we have completed an assessment of this diagnostic technique on 11 patients in whom choroidal melanoma was felt to be either certain (group 1) or a possibility (group 2).

Using the same labelling kit, Technemab (Sorin Biomedica), technetium-99m labelled F(ab')₂ fragments of MoAb 225 28S were injected. Images were recorded at 1 hour, 3 hours, and 6 hours after injection. Results were found to be most indicative at 6 hours, when the area of the affected eye was compared with the control eye. We found that the wearing of lead rimmed spectacles by the patient helped to delineate the area of the globe and allows accurate quantitative analysis.

Our results are presented in Tables 1 and 2. In three out of four patients with a clear diagnosis of melanoma there was a good correlation between other tests and histological proof. The fourth patient had a certain clinical diagnosis but refused enucleation. He has subsequently undergone iodine plaque irradiation. Radioimmunoscintigraphy in this case is therefore a presumed false negative. At a size of approximately 7 mm×7 mm this lesion was much the smallest in group 1. Table 2 shows that no clear pattern emerges in the four patients with naevi and possible malignant change. An equivocal result was obtained in patient 5 with a staphyloma; this was therefore a false positive.

Our current impression is that this test in its present form is not useful in the evaluation of patients with possible melanoma. We note, however, the identification of another

monoclonal antibody with a higher degree of specificity to melanoma, cytoplasmic antigen, which may warrant further investigation.²

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SIR, We thank Mr Tullo and colleagues for their interest. Since our first report we have carried out radioimmunoscintigraphy (RIS) on 54 patients with melanomas or simulating mass lesions in the ocular fundus. In our series, as in that described by Tullo *et al.*, it has not been possible to confirm histologically whether the diagnosis is melanoma or not in all cases. However, where enucleation was not considered justified there were strong clinical indicators that the diagnosis was correct, including ophthalmoscopic, fundus fluorescein angiographic, and B-scan ultrasound features. In these circumstances we have found the sensitivity of the test to be 93%, the specificity 95%, and the accuracy 96%. During this time we have refined the RIS technique and have gained experience in interpreting the computer-enhanced colour images obtained.¹

The correspondents do not indicate their criteria of positive, negative, or equivocal images and do not state whether these were based on a grey scale or on the colour images which we have found to have a higher positivity rate. On the basis of the relatively small number of presumed melanomas they report Tullo *et al.* have found a sensitivity which at 75% is slightly less than our value. They have found RIS positivity or equivocal results in two of four individuals with naevi and possible malignant change. In our initial communication we reported antibody uptake in an apparent benign naevus and stated that 'the immunoscintigraphy response of choroidal naevi remains to be investigated'.² We have since evaluated four ocular naevi which are known not to have changed for a minimum of five years. RIS was positive in two and negative in two. We do not know whether those naevi which show uptake are destined to undergo malignant change, and it is possible that the high molecular weight melanoma-associated antigen is expressed by benign naevi. Long-term follow up may resolve this issue,³ but in the meantime we would reiterate the clear statement in our preliminary communication that RIS should only be used to complement established diagnostic tests² and not in isolation. More recently we have stated our opinion that RIS cannot distinguish between various types of melanocytic lesion and that its use should be confined to differentiating between melanocytic and non-melanocytic tumours.⁴

In the course of time we hope to report significant numbers of RIS results with histological proof of the diagnosis of melanoma. However, because current management of melanoma makes enucleation hard to justify for small tumours, it will be difficult to provide cast iron proof of the diagnosis in other than large lesions. Furthermore, because we do not enucleate eyes with presumed benign

Table 1 Patients with malignant melanoma (group 1)

Patient	Sex, age	FA	USG	RIS	HISTOL
1	M, 45	+	+	+	+
2	M, 40	±	+	+	+
3	M, 49	ND	+	+	+
4	M, 40	+	+	-	-

FA=fluorescein angiography. USG=ultrasonography. RIS=radioimmunoscintigraphy. MM=malignant melanoma. ND=not done.

Table 2 Patients with various diagnoses (group 2)

Patient	Sex, age	Diagnosis	FA	USG	RIS
1	M, 65	Naevus	Early ? malignant change	-	+
2	M, 63			ND	±
3	F, 59			MM	-
4	F, 58			ND	-
5	M, 61	Staphyloma	ND	Staphyloma	±
6	F, 86	? Large MM	ND	±	-
7	M, 79	? Large MM	±	±	+

tumours, we will not find it easy to confirm histologically what we at present regard as true negative results. We agree with Tullo *et al.* that investigation of other antibodies is warranted. In vitro we found monoclonal antibody (MoAb) 763.24T to have greater affinity for melanoma cells than MoAb 225.28S.⁵

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Circulatory collapse and ROP

SIR, Ng *et al.* (*BJO* 1989; **73**: 111-4) report an association between circulatory collapse, the development of severe retinopathy of prematurity (ROP) and periventricular leucomalacia (PVL). They suggest that postnatal hypoxic/ischaemic brain and retinal injury may form a common pathway in the pathophysiology of severe ROP and PVL in predisposed infants, though no data on the cause, severity, frequency, or duration of the circulatory collapse are given.

This theory is indirectly supported by metabolic data published from our unit. The frequency and duration of episodes of arterial pH falling below 7.2 due to metabolic, respiratory, or mixed acidosis, and also the duration of episodes of both hypoxia (PaO₂ <5.5 kPa) and hyperoxia (paO₂ >12 kPa) were shown to be significant variables in the development of ROP.¹

Tissue hypoxia resulting from vascular insufficiency is a potent cause of metabolic acidosis, with consequent loss of cerebral and choroidal autoregulation and further loss of perfusion pressure, so it can be suggested that descriptions of circulatory collapse and descriptions of acidosis may refer to the same underlying processes. Quantified cotside measurements of cerebral blood flow using near infrared spectroscopy,² and continuous blood pressure monitoring are two techniques which may help to elucidate this important association further.

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SIR, We thank Messrs Acheson and Schulenburg for their interest in our article and also for their support for the idea that severe ROP and PVL may both be the consequence of cerebral circulatory hypoperfusion. We fully recognise the inadequacy of our data regarding the details of the circulatory collapse, but this is probably inevitable, as during this clinical catastrophe monitoring must necessarily take a back seat.

We are also looking at the metabolic risk factors for ROP. While on univariate analysis we obtained similar results,¹ using linear regression analyses for both the incidence and severity of ROP the variables PaO₂, pH, and PCO₂ failed to remain independently significant (in preparation). The relationship of metabolic acidosis to further loss of perfusion pressure remains speculative, and we are unable to comment further on this issue. The idea of prospectively continuously monitoring the cerebral blood flow and blood pressure to investigate this subject further is attractive but the logistics are probably overwhelming, as in our study this association developed in only 6 of the 299 infants at risk.

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Reference

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Book review

Clinical Ophthalmology: A Text and Colour Atlas. By JAMES L KENNERLEY BANKES. Pp. 130. £14.95. Churchill Livingstone: Edinburgh. 1987.

This is a very helpful book for the beginner in ophthalmology and hence should be of quite wide interest. Medical students are probably its principal target, but opticians might also find the book of interest as well as some general practitioners. It is probably of somewhat limited value to anyone specialising in ophthalmology, but even for this group a read through during the first few days of the first residency would certainly not come amiss. Definitely a good book to have in the library.

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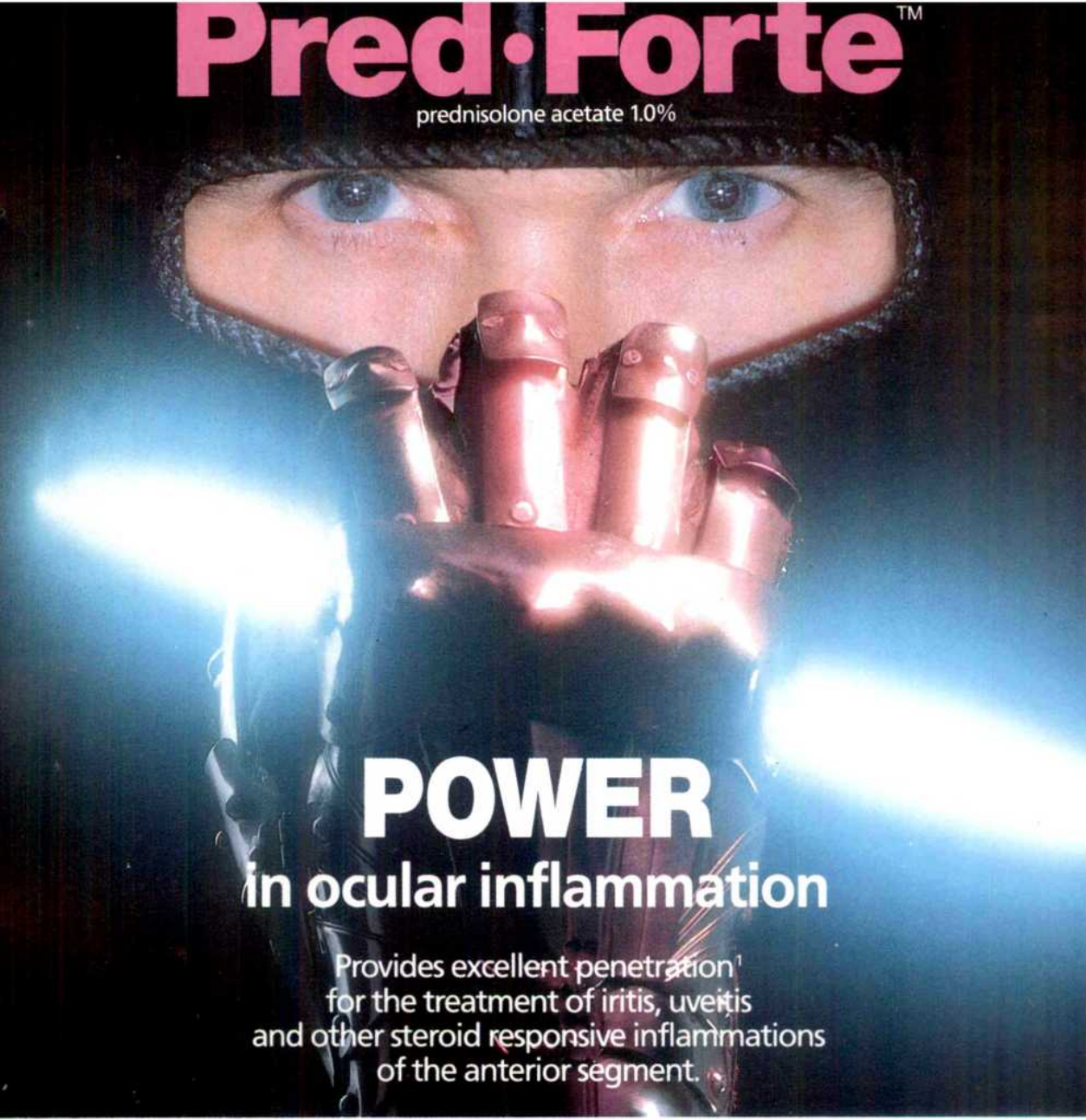
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Editorial: Aphakic detachment: a thing of the past?

Ophthalmologists trained in the late 1960s and thereafter can have no idea how pessimistic we who were trained earlier felt about aphakic detachment. So far as cataract surgery was concerned it was the flaw in the jewel, the great let-down. One was aware that it was unlikely to happen after an undisturbed extracapsular extraction, but with the perfunctory methods of capsulectomy and rudimentary attempts at anterior chamber 'washout' of those days not many extracapsular extractions escaped later capsulotomy, with its well known risk of precipitating retinal detachment; and the perfect intracapsular operation, with its beautiful black pupil and visual acuity correcting to 6/5 within a few days, was even more likely to precipitate detachment.

To make matters worse, although surgery for detachment was beginning to make great strides with the advent of scleral indentation procedures and the use of intraocular air (although vitrectomy was yet to come) one almost insuperable difficulty remained. The ophthalmologist could not see properly into the eye. Anyone who has tried to localise a hole with a direct ophthalmoscope after the removal of sub-retinal fluid (or even before it for that matter) will know what I mean. In contrast to the well illuminated hills and valleys and rivers and streams, albeit sometimes wreathed in mist, that one sees through an indirect ophthalmoscope, the direct ophthalmoscope will reveal a gloomy cavern with slate-grey walls looming over all and blackness in the depths. A good view of the hole or holes and of their relation to any diathermy, cryo or scleral indentation is almost impossible, and, as for air, that blacks out everything. If the situation was as bad as that with ordinary detachments it was ten times worse with aphakia, especially where there was much residual capsule.

Things are much better now. With all the present-

day techniques at his disposal the detachment expert expects to replace the vast majority of retinæ, albeit not always at the first attempt or with perfect visual results. But an eye with even poorish vision and a flat retina is infinitely to be preferred to one with detachment. Better still if the detachment does not occur in the first place, and this is where the article by Gray and his colleagues in this issue comes in. They have shown beyond reasonable doubt that a substantial reduction in aphakic detachment has occurred on the switch from intracapsular to modern extracapsular extraction. It would thus seem that a bonus has been added to the already high dividends resulting from the intraocular lens (IOL).

Before the advent of the YAG laser capsulotomy it was somewhat unusual for capsulotomy to be performed in eyes with an IOL. It could be done but was distinctly awkward, as a choice had to be made between an entry via the pars plana or a rather difficult approach through a peripheral iridectomy, if there was one, or even by pushing the edge of the dilated pupil aside and slipping the Ziegler's needle past the edge of the IOL.

Most surgeons would perform capsulotomy only if a really serious visual deterioration developed due to colonisation of the posterior capsule with metaplastic lens cells, so-called capsular thickening. However, with the advent of the YAG laser capsulotomy is now easier in IOL cases than in simple extracapsular cases, since the IOL helps to focus the laser beam. But a price apparently has to be paid. Gray and his colleagues have found that in the post-YAG years the incidence of detachment in such eyes rose slightly. However, it seems that even with a capsulotomy an eye with an IOL is safer from detachment than an intracapsular eye.

REDMOND SMITH

Editorial: Corneal storage

The first successful human corneal transplant performed in 1905 presented no storage problems: it was from an eye removed because of trauma. In the 1930s Filatov, realising that cooling prolonged the survival of endothelium by slowing metabolism and conserving energy, introduced short term preservation by storing eyes in the humid atmosphere of the so-called moist chamber at 4°C. This has been the traditional level, though corneas can be safely stored at lower temperatures, since the solutes in the aqueous and corneal tissue depress the freezing point of intraocular water to just below 0°C. However, a margin of safety must be allowed for variations in temperature within the refrigerator so that accidental freezing will not occur. Whole eye storage has been criticised because the endothelium is allowed to remain in contact with aqueous and its toxic waste products. It is now rarely practical because of the inevitable delay called for by HIV testing.

Cryopreservation was introduced in 1965. The excised cornea is placed in increasing concentrations of dimethyl sulphoxide (plus albumin and dextrose) before being frozen, and is stored at -197°C. The process of freezing and thawing requires a trained technician and so is expensive and complicated, while there have been an unacceptable number of primary graft failures.

A significant advance was made in 1976 when McCarey and Kaufman introduced a storage medium, eponymously labelled MK. This, in common with other media, is based on TC 199 tissue culture, with the addition of dextran or other oncotic agents which limit the degree of tissue swelling during storage. It allowed the use of corneas for up to four days after removal.

In 1984 Kaufman modified this medium by substituting chondroitin sulphate, a natural polymer, for dextran (the Japanese had used it 20 years earlier). This 'new' medium, K Sol, extended the use of donor corneas to six days after enucleation. Unfortunately the manufacturers have now withdrawn it from general use because some samples were found to be contaminated by infectious organisms. Similar media are undergoing clinical trial at the moment, notably one produced by Chiron, to which epidermoid growth

factor has been added (in experimental conditions it can cause mitotic figures in endothelial cells).

Doughtman in 1976 reported satisfactory results using cornea stored in organ culture at 37°C. The corneas can be safely used for up to 30 days. The technique has been modified and used extensively in Holland and, of late, in Britain. This extended storage helps in providing tissue matched material for patients who are at high risk of rejection.

In this issue of the *BJO* there is an important contribution to intermediate term storage by Taylor and Hunt from the MRC Laboratories in Cambridge. They point out that tissue culture media which maintain cell viability at physiological temperatures for short periods are not suitable for preservation at reduced temperatures. It is not necessary to support metabolism at reduced temperatures, as control of ion and water distribution between intra- and extracellular compartments is best achieved by solutions such as CPTES. The most important constituent of this solution is a pH buffer, 'TES', which maintains ion and water distribution by physical rather than metabolic means. Taylor and Hunt studied stromal thickness, endothelial integrity, and ultrastructure of rabbit corneas, and compared CPTES with Ringer's solution to which glutathione and bicarbonate had been added (we would have been more interested in MK for comparison). Corneas stored in CPTES were significantly thinner than in Ringer's - plus solution (GBR) and endothelium and ultrastructural studies were satisfactory. A minor observation (possibly for clinical use later) is that corneas stored in CPTES are slower in the 'temperature reverse response' by 80 minutes. The buffer TES is remarkably safe and has been used in washout solutions in kidney transplantations.

It is to be hoped that Taylor and Hunt will continue their studies, perhaps on the cat model. The rabbit cornea is not ideal, since the endothelium can regenerate, and indeed the rabbit can preserve a transparent cornea from which the endothelium has been removed. If they can elaborate on their studies, this apparently safe substance could well be introduced into clinical practice.

T A CASEY

Retinal detachment and its relation to cataract surgery

R H GRAY, A R EVANS, I J CONSTABLE, AND I L McALLISTER

From The Lions Eye Institute, 2 Verdun Street, Nedlands, Perth 6009, Western Australia.

SUMMARY In Western Australia during the period 1 January 1976 to 31 December 1987 1089 eyes of 1044 patients in hospital were operated upon for primary rhegmatogenous retinal detachment due to causes other than penetrating trauma. Of these eyes 295 (27%) were aphakic or pseudophakic. During this period the annual number of cataract operations in the State increased by a factor of 245%, while aphakic and pseudophakic retinal detachment operations rose by only 55%. The declining risk of retinal detachment following cataract surgery is attributed to improvements in microsurgical techniques. In 1983 and 1984 the incidence of aphakic and pseudophakic retinal detachments dropped significantly ($p < 0.05$). At about this time extracapsular cataract surgery became widespread in the State, and this may explain the observed fall in retinal detachment operations. Since 1984 the incidence has risen owing to the rapidly increasing prevalence of pseudophakia in the resident population.

Recent studies have shown the incidence of retinal detachment (RD) to vary from 8 to 13 per 100 000 of the population.¹⁻⁵ Aphakic retinal detachment constitutes approximately one-quarter of these.⁵⁻⁸

With the advent of microsurgical techniques and the introduction of extracapsular surgery postoperative complications such as RD may have declined, though it is well recognised that surgical or YAG laser posterior capsulotomy increases the risk.⁹⁻¹¹ This study was undertaken to determine what effect the changing pattern of cataract surgery in Western Australia (WA) has had on the overall incidence of RD in this State.

The remote WA population provided a good model for this study because all rhegmatogenous RDs within the State were referred to a small number of surgeons (and hospitals) in Perth and Bunbury, and their records were traceable. By excluding out-of-State referrals we believe that the figures are accurate for the resident WA population over the period studied.

Material and methods

Available data on all patients undergoing surgery for primary RD in the period 1 January 1976 to 31 December 1987 were obtained from hospital records for all centres equipped to carry out this

operation in the State. RDs that followed penetrating trauma were excluded, as were patients not resident in WA at the time of surgery.

The following information was obtained on each patient: age, sex, side affected, date and type of previous cataract surgery, date of posterior capsulotomy, and date of primary RD surgery. Figures for the total number of cataract operations each year were obtained from the Health Department of WA and population figures were obtained from the Federal Bureau of Statistics. The data obtained were analysed by Student's *t* test.

Results

Between 1976 and 1987 the WA population rose steadily from 1.17 million to 1.50 million, an increase of 28%. During the same period the number of cataract operations per year increased from 1089 to 3755, a rise of 245%. Over the same 12 years 1089 eyes of 1044 patients underwent primary RD surgery as defined above (Table 1). Information could not be obtained on a further 13 eyes, which were excluded from the study. Two hundred and ninety-five eyes were aphakic or pseudophakic (27.7%) and 794 were phakic (72.3%). Intracapsular extractions (ICCE) had been performed on all eyes presenting in 1976, while by 1987 the proportion had fallen to 40%, the remaining eyes having undergone extracapsular surgery (ECCE) (Fig. 1).

Table 1 State population (State pop) in millions, total cataract operations, primary retinal detachment operations and calculated retinal detachment incidence (RD incidence) for aphakic and phakic patients, 1976-87.

Year	State Pop.	Cataract operations	Primary RD RD operations	RD Incidence	
				Phakic	Aphakic
1976	1.17	1089	74	4.35	1.79
1977	1.20	1127	76	5.25	0.91
1978	1.22	1209	77	4.10	1.96
1979	1.24	1310	79	4.35	1.85
1980	1.27	1361	95	5.59	1.73
1981	1.30	1597	83	3.84	2.38
1982	1.34	1968	114	5.82	2.60
1983	1.36	2419	55	3.28	0.66
1984	1.38	2708	71	3.69	1.30
1985	1.41	3015	107	5.24	2.26
1986	1.46	3221	127	6.09	2.60
1987	1.50	3755	131	6.30	2.80

Of the 1044 patients 438 were female (42%). RD operations were carried out on 577 right eyes (53%). Bilateral RD surgery was carried out on 45 patients (4.3%). Aphakic/pseudophakic patients presented most commonly between the ages of 61 and 80 years, while phakic patients were usually 51-70 years, though a small peak was observed in the 21-30-year group.

Of the 218 eyes with RD that had undergone ICCE data on cataract and RD surgery dates were obtained for 209. RD surgery took place within one year in 82 of these (38%) (Fig. 2). Of the 49 eyes that had undergone ECCE without subsequent capsulotomy 26 had RD surgery within one year (53%) (Fig. 3).

RD surgery was carried out on 28 eyes that had undergone ECCE and delayed Nd-YAG capsulotomy, and 19 (68%) of these were within one year of the capsulotomy (Fig. 4).

The average frequency of RD in the State was 6.7 per 100 000 population per year (4.82 for phakic patients and 1.88 for aphakic/pseudophakic patients). In 1983 the incidence of aphakic/pseudophakic RDs fell to 0.66, and in 1984 it was 1.3. In the following years the incidence rose again (Fig. 5). When 1983 and 1984 were compared with the years before and since, the observed fall was statistically significant ($p < 0.05$).

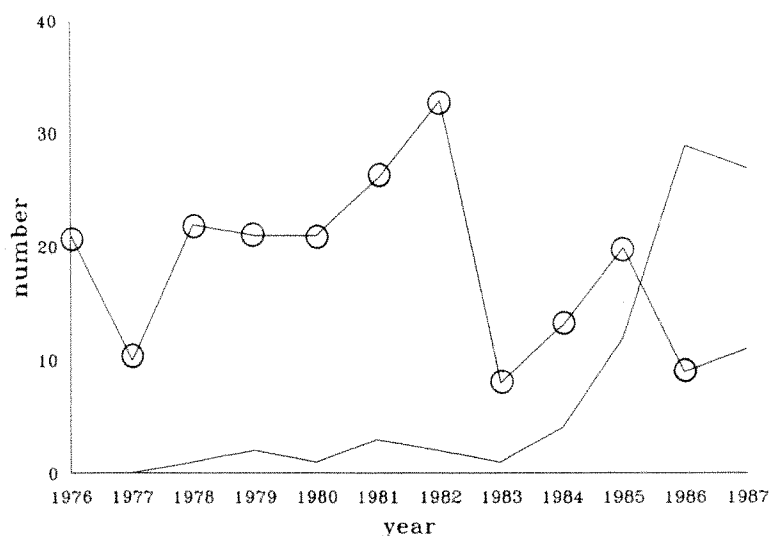
When the number of RD procedures performed on aphakic/pseudophakic eyes each year was compared with the number of cataract operations in the preceding year, the average risk of RD during 1976-82 was 1.75% (SD 0.4), while during 1983-7 it fell to 0.86% (SD 0.31) (Fig. 6).

Discussion

While the number of cataract operations per year has increased dramatically between 1976 and 1987 in this State, by a factor of 245%, the incidence of aphakic/pseudophakic RD has risen by only 55% (1.8 per 100 000 in 1976 rising to 2.8 in 1987).

The age distribution of our patients is similar to that of other studies,^{2,3,12} as is the slightly higher incidence of RD surgery on the right eyes of both phakic and aphakic/pseudophakic patients.^{2,5,8} The 4.1% incidence of bilaterally affected eyes is similar to that found in a previous study³ but lower than that in a larger study by Ashrafzadeh *et al*¹² who found the

Fig. 1 The yearly numbers of primary retinal detachment operations for 295 eyes that underwent intracapsular (○) or extracapsular surgery (—).



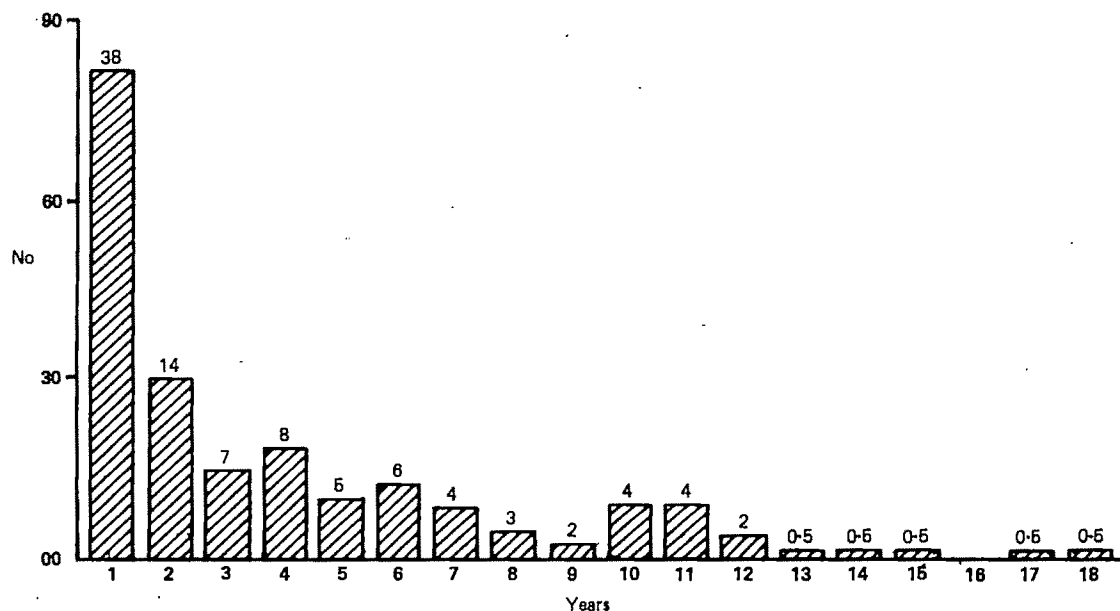


Fig. 2 Time interval to retinal detachment surgery for 209 eyes from the date of intracapsular cataract surgery (% of total above each bar).

incidence of bilaterally affected eyes to be 36.8% for aphakic and 31.2% for phakic eyes. This much higher figure may be partly explained by their inclusion of subclinical cases.

Our figures have shown that the risk of RD following cataract surgery is maximal in the first year, this being true for both ICCE and ECCE groups. This similarity has been reported elsewhere.¹³⁻¹⁵ In a post-mortem study of aphakic and pseudophakic

human eyes Osterlin found¹⁶ a significant deficit of hyaluronic acid only in those eyes operated upon by the intracapsular technique. The increased liquefaction of vitreous gel that this causes was thought by Binkhorst¹⁷ to be a significant factor in the causation of RD. But the striking similarity between ICCE and ECCE in terms of the interval to detachment, found in this and other studies, argues against the importance of this factor.

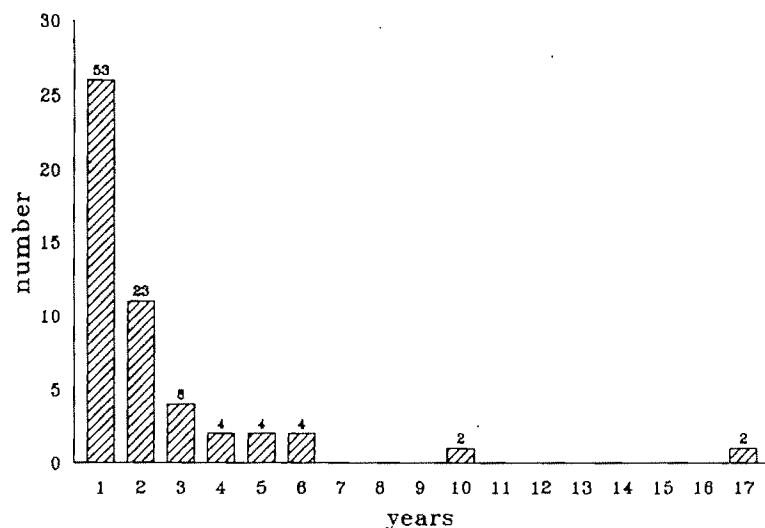
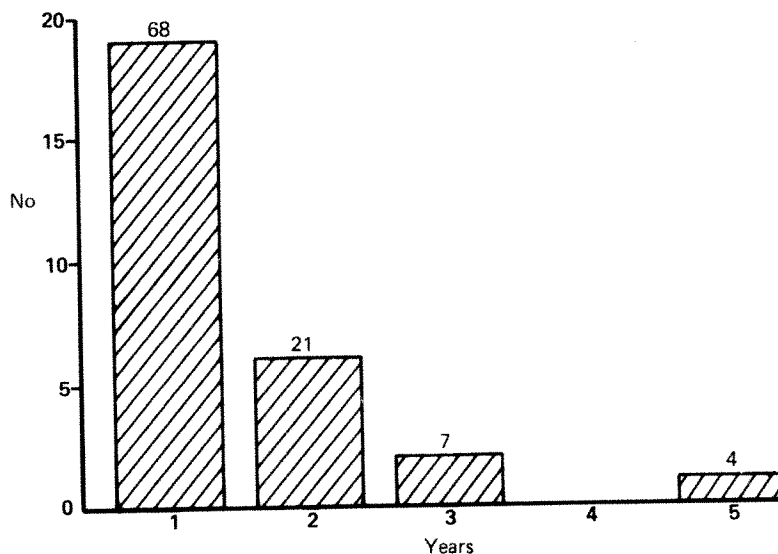


Fig. 3 Time interval to retinal detachment surgery from the date of cataract surgery for 49 eyes that underwent extracapsular extraction without subsequent posterior capsulotomy (% of total above each bar).

Fig. 4 Time interval to retinal detachment surgery from the date of Nd-YAG capsulotomy for 28 eyes following extracapsular cataract surgery (% of total above each bar).

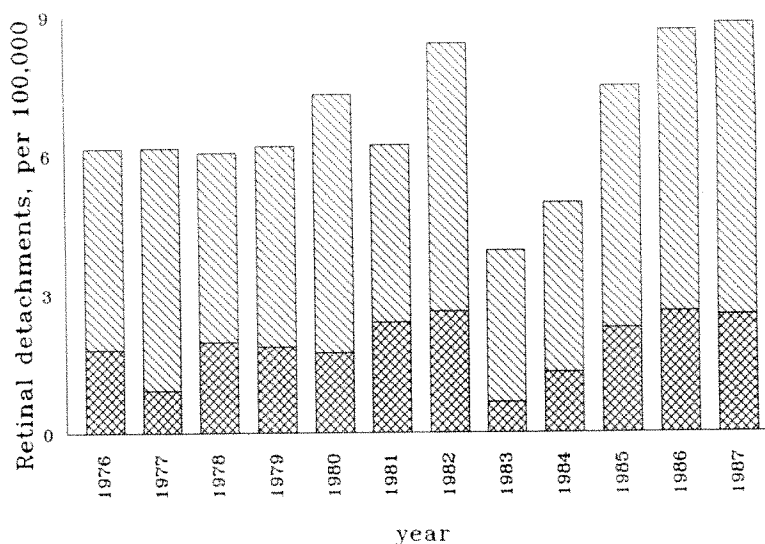


Of the 79 eyes that had RD surgery following extracapsular surgery in our group 28 had a posterior capsulotomy present (36%). As expected, most RDs following this procedure occurred within one year, in agreement with a previous study.¹⁸ We have no accurate figures for the number of Nd-YAG laser procedures carried out during the study period and cannot therefore comment on the risk of RD from this procedure, but three large studies^{9,10,19} have found the incidence of RD following YAG capsulotomy to be 0.5%, 1%, and 2% respectively. The importance of posterior capsulotomy, whether

primary or delayed, surgical or laser, is further evident from the 3.6% RD risk reported by Wilkinson *et al* on 1500 eyes that underwent ECCE with phacoemulsification.²⁰ Posterior capsulotomies were carried out on 94.7% of these eyes, and the authors comment on the similarity of this group to cases of intracapsular aphakia. We attribute the slightly higher risk of aphakic/pseudophakic RD since 1983 in our study to increasing availability and use of the Nd-YAG laser.

The average frequency of RD during the study period was 6.7 per 100 000 population per year

Fig. 5 Incidence of retinal detachment, per 100 000 of population, for phakic patients (▨) and aphakic/pseudophakic patients (■), 1976-87.



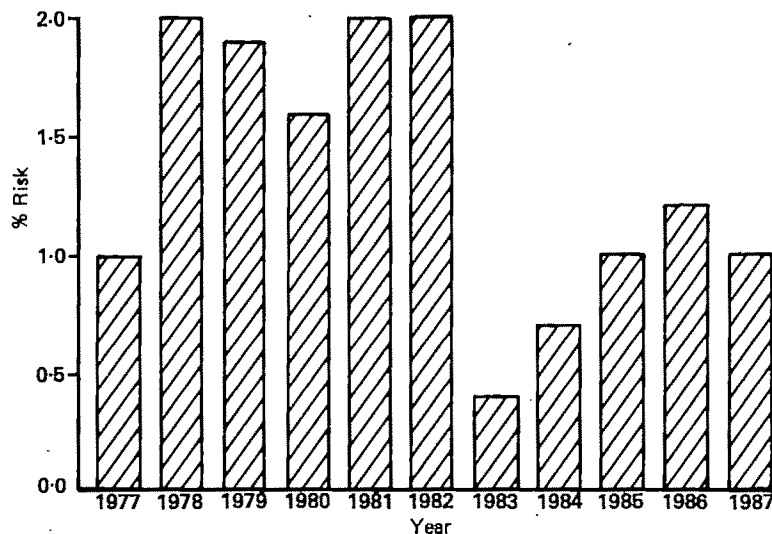


Fig. 6 Calculated risk of retinal detachment following cataract surgery, 1977-87.

This figure is broadly similar to those of other studies,^{2,3,5} and some of the differences may be attributable to the varying prevalence of aphakia, and possibly myopia, in the populations studied.

Between 1982 and 1983 almost all cataract surgeons in this State changed to extracapsular surgery, and a statistically significant fall in aphakic and pseudophakic RDs followed this change. We believe this provides good evidence that extracapsular surgery protects against RD when compared with ICCE. In a comparison of RD risk for 122 myopic eyes that underwent ICCE, with 151 eyes undergoing ECCE (both without vitreous loss) Jaffe *et al*²¹ found the risk in the former group to be 5.74% and in the latter only 0.66%. Minimum follow-up was one year. Coonan *et al* studied 842 consecutive ECCEs with a minimum follow-up of one year and found the overall risk of RD to be 1.4%.¹³ In uncomplicated cases in which the posterior capsule was left intact the risk was only 0.8%. In another study of 3065 cases of ECCE the risk was 1.7%, with a minimum follow-up of one year.¹⁴ Hurite *et al* studied 2095 patients who underwent ECCE by phacoemulsification, and the overall risk was 1.6%, with minimum follow-up of one year.²² The risk was only 1.2% for those cases in which the posterior capsule was left intact.

Accurate assessment of the risk of RD following cataract surgery is dependent on prolonged follow-up of a defined population. Such was not the case in this study. Nevertheless, bearing in mind that most RDs occur within the first two years, we believe our comparison of the number of aphakic/pseudophakic RDs per year with the total number of cataract operations for the previous year to be valid. The risk

of RD over the study period has fallen from a mean of 1.75% in the early part of the study to a mean of 0.86% in the years since 1982. At least some of this reduction is due to improved microsurgical techniques, and in particular the avoidance of vitreous loss. Though this retrospective study had not yielded reliable data on vitreous loss, other studies have confirmed its importance.^{13,20,22}

This study has documented the incidence of primary retinal detachment surgery during a period of major change in the surgical management of cataract. We have shown that the number of RD operations has risen much less than the number of cataract operations, and we attribute this to improvements in microsurgical techniques. The statistically significant fall in the number of aphakic/pseudophakic RD operations which began in 1983 may be attributable to the introduction of extracapsular cataract surgery a short time before.

We are grateful for the assistance of Dr Valerie Alder for statistical analysis of the data.

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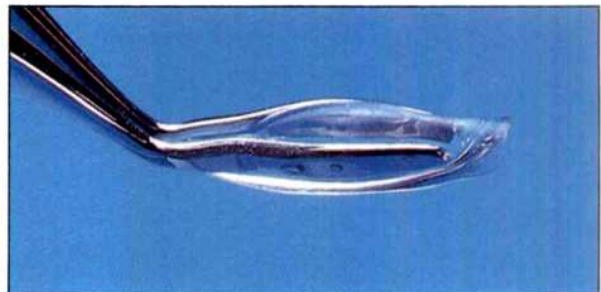
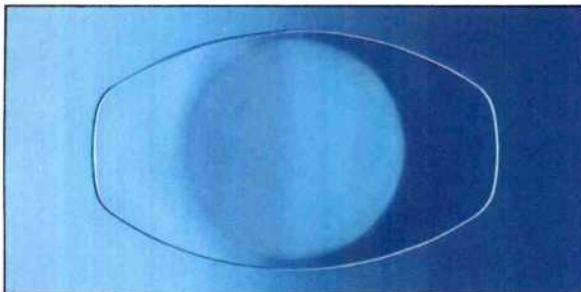
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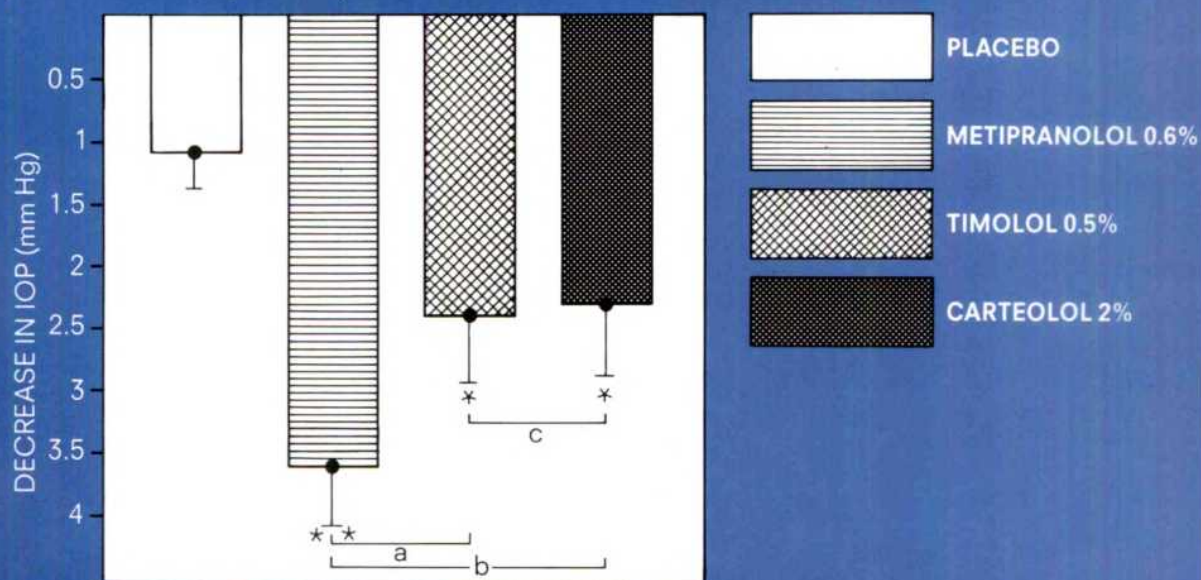
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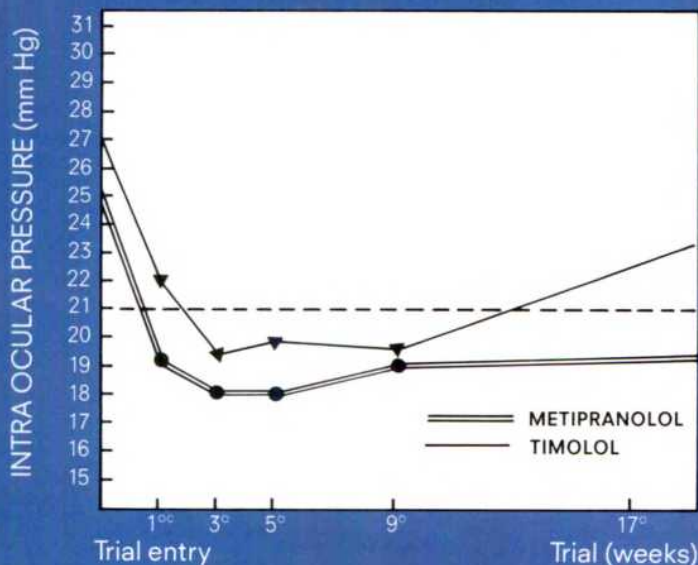
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(b) In a middle term study²



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ALLERGAN PHARMACEUTICALS

SCIENCE WITH VISION

Hypothermic preservation of corneas in a hyperkalaemic solution (CPTES): I. Short-term storage in the absence of colloid osmotic agents

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SUMMARY Preservation solutions for short-term storage of isolated donor corneas for use in penetrating keratoplasty have all been based on tissue culture medium, on the assumption that media designed to maintain the viability of cells at physiological temperatures will also provide suitable conditions for preservation at reduced temperatures. But for hypothermic preservation of some other tissues and organs, when ionic pumps are inhibited, it is unnecessary to support metabolism, and beneficial control of ion and water distribution between intra- and extracellular compartments is achieved by storage in appropriately formulated 'intracellular-type' solutions. We have therefore designed a solution that will restrict ionic imbalances and minimise endothelial cell swelling in corneas during exposure at reduced temperatures. This potassium-rich solution contains the biological pH buffer TES as an impermeant anion and is designated CPTES (corneal-potassium-TES). The structural and functional integrity of rabbit corneas stored at 0°C in CPTES, without the addition of colloid osmotic agents, is compared with that of corneas stored in glutathione bicarbonate Ringers' solution (GBR), an 'extracellular-type' medium formulated for the maintenance of endothelial integrity during in-vitro perfusion at 34°C. Corneas swelled significantly less during storage in CPTES than in GBR and could be stored for five days before reaching the same degree of hydration as corneas stored for only three days in GBR. Gross structural integrity and endothelial ultrastructure were maintained during storage for three and five days in CPTES. The rate of thinning of corneas stored in CPTES was significantly greater than in comparable groups of corneas stored in GBR. However, the efficient dehydration of corneas stored in CPTES was always preceded during perfusion by a brief period of additional swelling which was shown to be an osmotic response during the elution of the buffer compound TES that had permeated the stroma during storage. The omission of calcium or the addition of adenosine and glutathione to the CPTES preservation medium had no detectable effect on the integrity of the endothelium, but the omission of bicarbonate was beneficial, producing significantly higher rates of stromal thinning during normothermic perfusion. Additional benefits for extending storage by including colloid osmotic agents are described in a companion paper.

Preservation of some biological tissues at reduced temperatures succeeds because cooling prolongs in-vitro survival by slowing metabolism, reducing the demand for oxygen and other metabolites, and by

conserving chemical energy.¹ Historically the short term preservation of corneas has been achieved by storing enucleated eyes in the humid environment of a so-called moist chamber at 4°C. The accepted time limit imposed on this method of storage is 24–48 h.² However, storage of corneas while still an integral part of the eyeball has been questioned, because

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post-mortem changes in the composition of the aqueous humour are known to make it unsuitable, even toxic, as a medium for bathing the endothelium during storage.^{3,4} Furthermore, swelling of the cornea during 4°C storage makes it difficult to achieve contiguity of the graft with the host bed. Such problems have led to the practice of excising the cornea and storing it in a suitable medium separated from the eyeball.²

However, adoption of storage techniques in clinical practice has often proceeded in advance of the establishment of a firm specification for what constitutes a suitable medium for hypothermic storage of corneas. In the past decade preservation solutions have been based on TC199 tissue culture medium with the addition of either dextran (M-K medium),⁶ polyvinylpyrrolidone,⁷ or glycosaminoglycans (K-SOL)^{8,9} as oncotic agents to limit the degree of tissue oedema during storage. With this approach effective preservation of corneas for penetrating keratoplasty has been extended to about one week.¹⁰ However, the particular balance of ions and molecules in tissue culture medium is designed to maintain the metabolic status of cells *in vitro* at physiological temperature and therefore will not be optimal for maintaining the ionic and hydraulic balance within corneal endothelium at reduced temperatures.

An approach that has proved beneficial in the hypothermic storage of organs and other tissues assumes that, at reduced storage temperatures, it is unnecessary to support metabolism, and that the normal distribution of water and ions between the intracellular and extracellular compartments can be maintained by physical rather than metabolic means.¹ Since during the period that metabolic pumps are inactivated the driving force for sodium loading and potassium depletion from the cells is the difference in ionic balance between the intra- and extracellular fluid, and the driving force for water uptake (cell swelling) is the impermeant intracellular anion, these changes should be prevented or restricted by immersion of the tissue in an appropriate 'intracellular-type' solution.

With this objective in mind we have advocated the use of a hyperkalaemic balanced salt solution (CPTES) containing an impermeant anionic buffer, N-tris (hydroxymethyl) methyl-2-aminoethane sulphonic acid (TES), as an appropriate bathing medium for the low temperature preservation of corneas.¹¹ The sulphonic acid buffer, TES, is one of a family of zwitterionic compounds which have found widespread use as highly effective biological pH buffers at both physiological and reduced temperatures.¹²⁻¹⁴ The potassium-rich CPTES solution containing 100 millimolar TES was designed

primarily as a suitable medium for adding and removing cryoprotectants during procedures for the long term cryopreservation of corneas, and has been shown to be an effective 'vehicle' solution for adding and removing multimolar concentrations of dimethyl sulphoxide in isolated rabbit corneas at 0°C.^{11,15} The purpose of this investigation was to evaluate the merits of CPTES as a solution for intermediate-term storage at 0°C in the absence of cryoprotective agents.

In this paper the structural and functional integrity of corneal endothelium is examined after one or three days' storage at 0°C in CPTES and is compared with that of corneas stored under similar conditions in glutathione bicarbonate Ringer's solution (GBR), and 'extracellular-type' balanced salt solution formulated for the maintenance of endothelial integrity during *in-vitro* perfusion at 34°C.^{11,16,17} Endothelial integrity was also examined after five days' storage in CPTES at 0°C. Parameters studied in the evaluation of corneal integrity at the end of storage include the initial stromal thickness immediately following storage, corneal hydration changes during *in-vitro* perfusion on the specular microscope, and corneal endothelial cell ultrastructure.

Studies which examine extended storage in CPTES with the addition of colloid osmotic agents are described elsewhere.^{18,19}

Material and methods

Corneas were excised from the enucleated eyes of New Zealand White rabbits (2-3 kg) as previously described.¹¹ For storage at 0°C polypropylene vials containing 5 ml of the preservation medium were placed in an evacuated Dewar flask containing ice which was itself placed in a 4°C refrigerator for the storage period. Isolated corneas, supported on plastic rings, were immersed endothelial side uppermost in the precooled storage solution. At the end of the storage interval corneas were either mounted in the perfusion chamber of a specular microscope to assess endothelial function or processed for microscopy as described previously.^{11,15}

In the standard procedure for specular microscopy isolated corneas were perfused for 6 h at 34°C with glutathione bicarbonate Ringers' solution (GBR) as previously described.¹¹ In some cases, as indicated below, alternative perfusion solutions were used to assess particular aspects of stromal swelling and hydration during specular microscopy. The ionic composition of these various solutions is given in Table 1, and the precise formulation of CPTES in terms of both the weight and millimolar concentrations of the constituent salts and other chemicals is provided in Table 2.

Table 1 Composition of solutions (mmol/l)

	Rabbit aqueous humour*	GBR	CPTES	GBR/TES	BCFR
Na ⁺	143.0	158.48	31	129.82	151.4
K ⁺	4.7	4.82	100	4.82	6.75
Cl ⁻	107.9	136.77	32	38.44	149.87
HCO ₃ ⁻	31.9	29.16	30	29.16	—
H ₂ P ₄ O ₇	0.7	0.66	1	0.66	1
HPO ₄ ²⁻	—	—	—	—	4.2
SO ₄ ²⁻	0.6	—	0.78	0.78	0.6
Mg ²⁺	0.5	0.78	0.78	0.78	0.6
Ca ²⁺	1.4	1.03	1.03	1.03	0.56
Glucose	5.6	4.99	5.0	4.99	4.45
Reduced glutathione	—	0.29	(0.29)†	0.29	1.0
Adenosine	—	0.50	(0.50)†	0.50	—
TES	—	—	100	100	—
Osmolality (mosm.kg ⁻¹)	310	320	301	312	310
pH	—	7.4	7.7	7.6	7.4

TES: N-tris (hydroxymethyl)methyl-2-aminoethane sulphonate. Application of the Henderson-Hasselbalch equation for the dissociation of this zwitterionic buffer in the CPTES medium shows that 62% of the TES is in the anionic form.

GBR: Glutathione bicarbonate Ringer's solution.

CPTES: Potassium-rich, TES buffered corneal preservation solution.¹¹

GBR/TES: GBR with 100 mmol/l Cl⁻ replaced with TES.

BCFR: Bicarbonate-free Ringer's solution.

*From Kinsey.²⁰ †Ingredients given in parentheses are normally absent but included in specific experiments as indicated.

The structural integrity of the endothelial layer was assessed by light microscopy after vital staining with trypan blue and alizarin red S.²¹ Ultrastructural examination of the endothelium in some stored corneas was carried out using transmission electron microscopy as described previously.¹⁵

STORAGE CONDITIONS

Endothelial integrity was evaluated after storage for either one or three days at 0°C in either GBR or CPTES solutions having the compositions given in Table 1. Additional groups of corneas were stored for

three days in similar solutions having the following minor modifications to their formulation:

CPTES without the addition of CaCl₂; CPTES with the addition of adenosine and reduced glutathione in the concentrations normally present in GBR; bicarbonate-free GBR and bicarbonate-free CPTES in which the NaHCO₃ (30 mmol/l) was replaced with 30 mmol/l NaCl; and finally GBR/TES in which 100 mmol/l of chloride in the standard GBR solution was replaced with 100 mmol/l TES. One additional group of corneas was stored in CPTES at 0°C for five days.

ANALYSIS

As in previous studies,^{41,45} measurements of stromal thickness for individual corneas were scheduled at the same time intervals during perfusion, and the change in thickness was normalised with respect to initial values determined immediately after enucleation. This procedure enabled mean percentage changes (± 1 SEM) in stromal thickness for a group of corneas treated in a particular way to be evaluated as a mean normalised response curve. The rate of stromal swelling or thinning during perfusion was calculated from a regression analysis of the response curves to provide a measure of the efficiency of the endothelia in controlling stromal hydration. The Tukey-Kramer method for unplanned comparisons was used as described by Sokal and Rohlf²² for comparing regression coefficients in this analysis.

Table 2 Formulation of CPTES: a hyperkalaemic preservation medium for the cornea

Ingredient	g/l or ml/l	mmol/l
NaHCO ₃	0.520 g	29.996
NaH ₂ PO ₄ ·2H ₂ O	0.156 g	1.000
MgSO ₄ ·7H ₂ O	0.192 g	0.780
CaCl ₂ ·6H ₂ O	0.226 g	1.030
Glucose	0.901 g	5.000
TES* (free acid)	22.920 g	100.000
Potassium hydroxide (1 N KOH stock)	100 ml	100.000
Hydrochloric acid (1 N HCl stock)	30 ml	30.000

Total osmolality=301 mosm/kg. pH=7.7 after gassing with O₂/CO₂ (95%/5%).

*TES: N-Tris (hydroxymethyl)methyl-2-aminoethane sulphonic acid (crystalline free acid; Sigma Product No. T-1375).

Results

EXTENT OF CORNEAL SWELLING DURING STORAGE

In all experiments the initial thickness of each cornea was measured *in situ* before dissection by mounting the enucleated eye under the specular microscope. The mean thickness of the corneas used in these experiments was $317 \mu\text{m}$ ($\text{SD} = \pm 23$).

Fig. 1 shows the mean increase in stromal thickness sustained by each of the groups of corneas during storage at 0°C when the metabolic pumps responsible for normal control of tissue hydration are impaired or retarded. Corneas stored overnight in GBR swell to the same extent as that reported for rabbit corneas that were stored in moist chambers without excision from the whole eye. Under these conditions the endothelium was bathed throughout with aqueous humour.^{23,24}

Corneas stored for the same length of time in CPTES (with or without Ca^{2+}), however, swell only about half as much; that is, corneas stored in CPTES were significantly thinner than those stored in GBR ($p < 0.005$). Similarly, after three days' storage the swelling of corneas bathed in CPTES was significantly

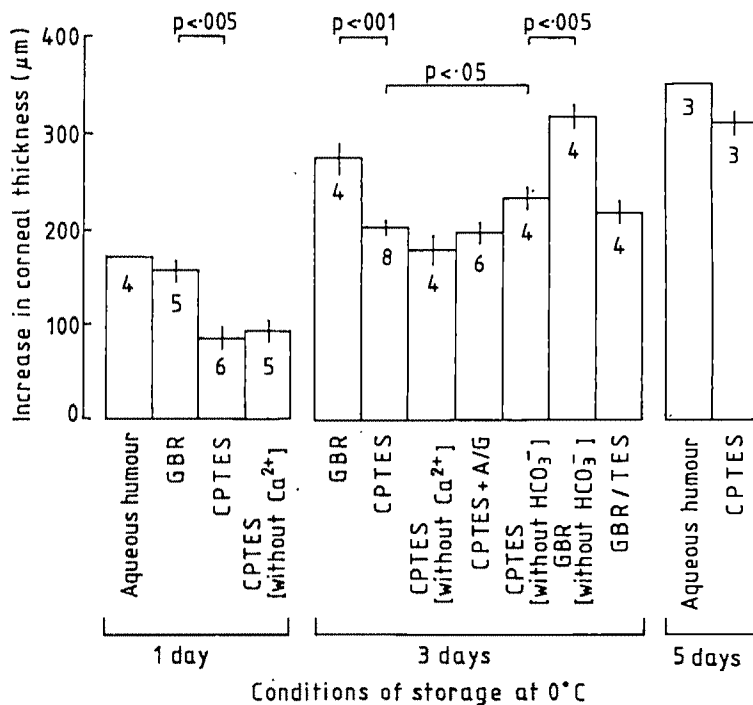
less than for the corresponding group of corneas stored in GBR ($p < 0.001$). The omission of calcium or the addition of adenosine and reduced glutathione did not influence the degree of swelling in corneas stored in CPTES for three days at 0°C (Fig. 1). The omission of bicarbonate, however, led to higher mean thicknesses for groups of corneas stored in either CPTES or GBR. Corneas stored in GBR/TES swelled significantly less than corneas stored in normal GBR ($p < 0.05$); the extent of swelling was equivalent to storage in CPTES. Fig. 1 also shows that corneas stored in CPTES do not double in thickness until after five days' storage, whereas corneas stored in GBR attain this degree of swelling in only three days.

MORPHOLOGY

Light microscopy

The structural integrity of corneal endothelium was retained following storage in CPTES for three and five days at 0°C . Examples of the intact endothelia observed both immediately after five days' storage at 0°C and after a further four hours' perfusion at 34°C are shown in Fig. 2A and B respectively.

Fig. 1 Changes in stromal thickness during storage for corneas bathed in various solutions at 0°C . The mean ($\pm 1 \text{ SEM}$) increase in thickness and the number of corneas measured in each group are represented in each histogram. Data for corneas stored in aqueous humour were taken from Sherrard.^{23,24} Statistically different levels of corneal swelling are indicated (Student's *t*-test).



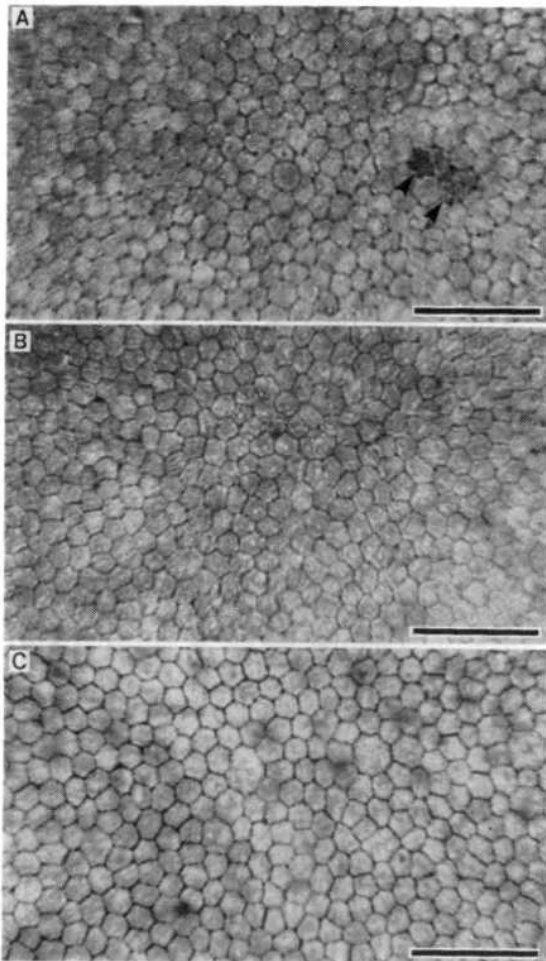


Fig. 2 Light microscopy of corneal endothelium after staining with trypan blue and alizarin red S. A: Specimen stained immediately after five days' storage in CPTES at 0°C. Very few areas of endothelial damage could be located on corneas stored in this way; a small isolated group of 'damaged' cells is arrowed. B: Specimen stored for five days in CPTES at 0°C and stained after a further four hours perfusion with GBR at 34°C showing a completely intact endothelium, and none of the cells were permeable to trypan blue. C: Fresh cornea perfused with GBR/TES for six hours at 34°C. Scale bar is 100 µm.

Ultrastructure

After three days' storage in either GBR or CPTES corneas showed a normal endothelium in close apposition to Descemet's membrane (Fig. 3A,B). There was some slight oedema localised within the interdigitated cellular processes of the basal region after both treatments, while samples stored in GBR also showed slight swelling of rough endoplasmic

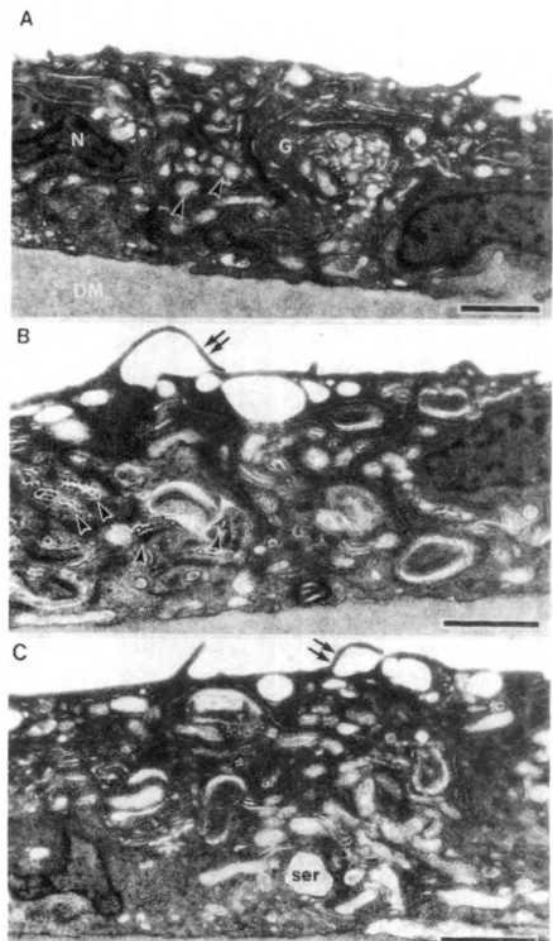


Fig. 3 Endothelial ultrastructure following storage at 0°C. A: Three days' storage in GBR; endothelium is closely apposed to Descemet's membrane (DM) and shows invaginated nuclei (N), a well developed Golgi apparatus (G), and slight swelling of some mitochondria (arrowed). B and C: Three and five days respectively in CPTES; mitochondria show moderate swelling with diffuse pallid matrices as well as condensed and beaded forms (arrow heads), vesiculated smooth endoplasmic reticulum (ser), and raised apical flaps (double arrows). Apical junctions are closed. Scale bar is 1 µm.

reticulum, increased invagination of the nucleus, and a distinct proliferation of Golgi vesicles. Mitochondria showed similar reversible changes in corneas stored in both GBR and CPTES.

After five days' storage in CPTES (Fig. 3C) the endothelium was moderately swollen, and in a small number of samples there was minor localised detachment from Descemet's membrane, though apical

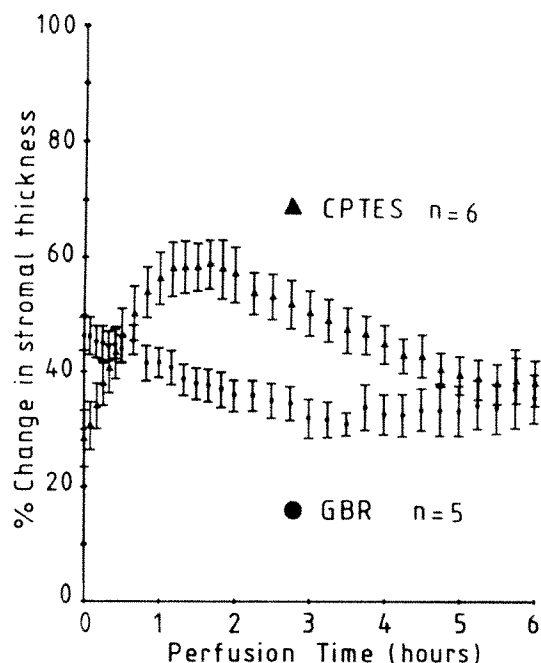


Fig. 4 Mean stromal hydration changes during perfusion for groups of corneas after storage for one day in either CPTES ($\blacktriangle$) or GBR ($\bullet$) at 0°C . The biphasic curve for corneas stored in CPTES is explained in the text; these corneas thinned at 5.6 ($\text{SEM } 0.2$)% per hour. Corneas stored in GBR thinned at 4.8 ($\text{SEM } 0.2$)% per hour. Sherrard has previously shown that the criterion for a viable cornea is a 'temperature reversal' rate of $25\text{ }\mu\text{m}$ in two hours ($\sim 4\%$ per hour).²⁴

junctions remained closed. Most organelles showed similar changes to those seen after three days' storage, though now smooth endoplasmic reticulum was swollen and vesiculated. The state of the endothelium after storage for three days in GBR and up to five days in CPTES would suggest that, immediately after storage, no irreversible changes had occurred to the majority of cells.

CHANGES IN STROMAL HYDRATION DURING PERFUSION

Fig. 4 shows contrasting responses for corneas stored in CPTES compared with those stored in GBR. The marked difference in stromal thickness at the beginning of perfusion following storage at 0°C is clearly apparent; thereafter corneas which had been bathed in GBR during storage decrease in thickness during subsequent perfusion at 34°C . This response is commonly referred to as the 'temperature reversal' response, since it describes the characteristic reversal of swelling by the reactivation of endothelial-pump

activity when the tissue is rewarmed to physiological temperature. Corneas stored in CPTES did not 'temperature reverse' immediately, but showed a biphasic response in which they initially underwent further swelling during the first 90 minutes of perfusion. Thereafter, they decreased in thickness by 5.6 ($\text{SEM } 0.2\%$) per hour, demonstrating the activity of fully functional endothelia. Similarly, Fig. 5A shows that, for the group of corneas stored for three days in CPTES at 0°C an identical rate of thinning was preceded by stromal swelling for 90 minutes when these corneas were perfused with GBR at 34°C . An additional group of corneas were stored in CPTES for three days and then perfused at 34°C for two hours with GBR followed by bicarbonate-free medium (BCFR) for a further four hours. Fig. 5B shows that during the second phase of perfusion, when the bicarbonate pump was switched off, these corneas did not thin but swelled further, thus confirming that the deturgescence recorded during the second phase for those corneas perfused throughout with GBR (Fig. 5A) was due entirely to active endothelial pumping.

When corneas stored under identical conditions were perfused with GBR/TES instead of GBR they did not swell at the beginning of the perfusion. Fig. 5A shows that these corneas began thinning immediately and eventually reached a plateau at a constant thickness throughout the remaining period of perfusion. The role of a functioning endothelium in controlling the hydration of these corneas is further demonstrated in Fig. 6 by induced swelling when the preparation was perfused with medium that does not contain CO_2 or bicarbonate ions (BCFR/TES).¹⁸ Under these conditions the bicarbonate-dependent pump is inactivated and the cornea swells at $25\text{ }\mu\text{m/h}$. This swelling was reversed at the same rate when the cornea was again perfused with GBR/TES. Fresh corneas perfused with GBR/TES alone for six hours retained the integrity of the endothelial layer as illustrated in Fig. 2C.

Corneas stored for three days in GBR at 0°C showed a normal 'temperature reversal' response when perfused with GBR at 34°C (Fig. 7). However, corneas stored at 0°C for three days in GBR containing 100 mmol/l TES (GBR/TES) showed a biphasic response during subsequent perfusion with GBR at 34°C that was similar to that of corneas stored in CPTES and perfused with GBR. Fig. 7 shows that initially the stroma swelled for 90 min before an active dehydrating mechanism was apparent.

Corneas stored for three days at 0°C in CPTES containing the same concentrations of glutathione and adenosine as in GBR, or stored in CPTES with the omission of calcium, showed identical responses during perfusion as the group of corneas stored in the

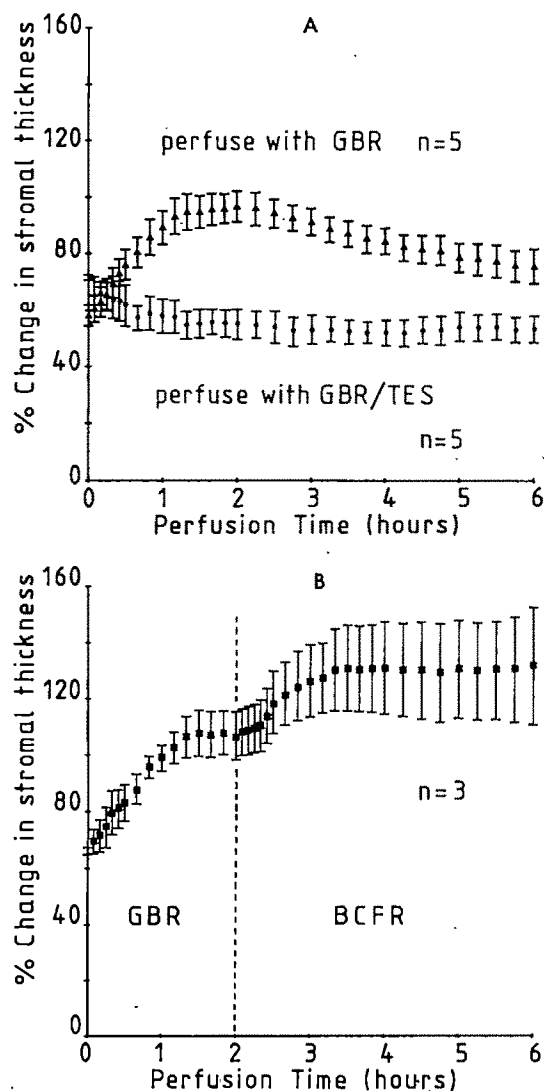


Fig. 5 Stromal thickness changes for corneas stored in CPTES for three days at 0°C. A: Mean response curves for groups of corneas perfused at 34°C under the specular microscope with either GBR (Δ) or GBR/TES ($\bullet$). B: Mean response curve for a group of corneas when perfusion with GBR was changed after two hours to perfusion with bicarbonate-free Ringer's solution (BCFR) as indicated by the broken line.

standard CPTES solution. Fig. 8 shows that the stromal thickness curves can be superimposed, having the same biphasic profile as that shown in Fig. 5A for corneas stored in CPTES. Corneas stored in CPTES containing Ca^{++} thinned at 5.6 (SEM 0.2)% per hour (n=5), which was not significantly different from the

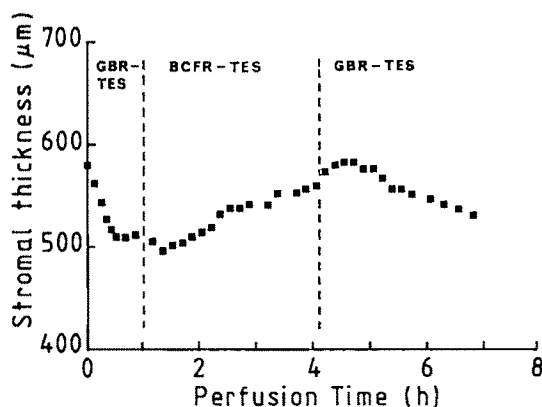


Fig. 6 Endothelial pump activity in a cornea stored in CPTES for three days at 0°C. Perfusion with GBR/TES was interrupted by perfusion with BCFR/TES which contained no bicarbonate or CO_2 . Broken lines represent the points at which solutions were changed. See text for interpretation of these curves.

group of corneas stored in CPTES without calcium (5.9 (SEM 0.2)% per hour, n=4). However, the corneas stored in CPTES with adenosine and glutathione thinned at 6.4 (SEM 0.1)% per hour (n=6) which was not significantly different from the Ca^{++} -

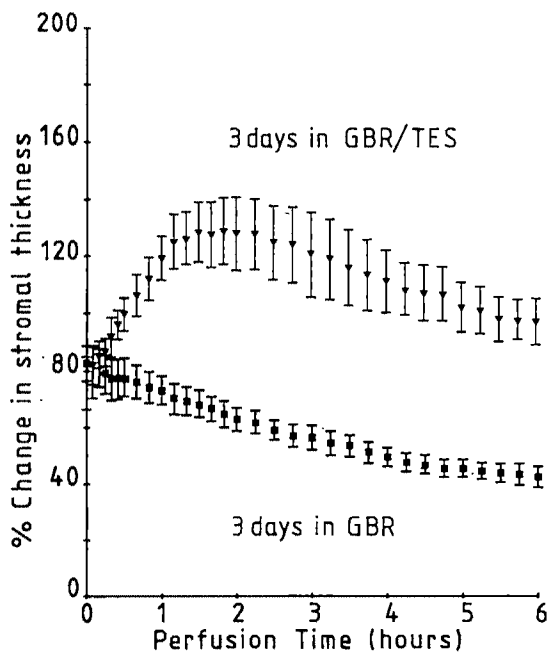


Fig. 7 Mean stromal thickness curves for groups of corneas stored for three days at 0°C in either GBR ($\blacksquare$), n=4; or GBR/TES ($\blacktriangledown$), n=3. Both groups of corneas were perfused with GBR at 34°C.

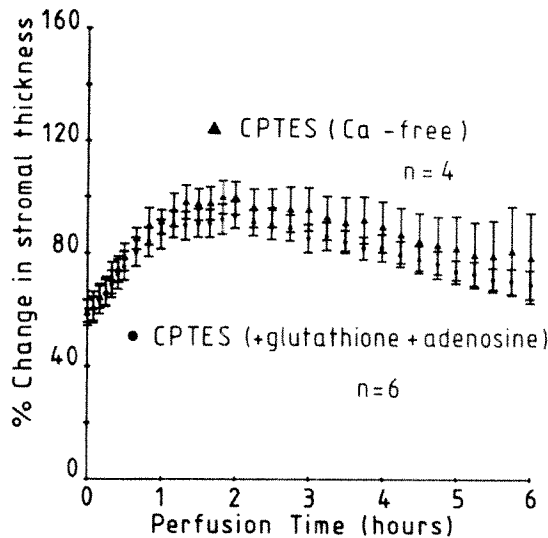


Fig. 8 Comparison of the mean stromal thickness curves derived for groups of corneas after storage for three days at 0°C in either calcium-free CPTES (▲) or CPTES containing glutathione and adenosine (●). All corneas were perfused at 34°C with GBR.

free group but was significantly different from the group stored in CPTES when compared at the 95% level but not the 99% level of confidence (Table 3).

The endothelium of corneas stored for three days in solutions from which bicarbonate was omitted dehydrated the swollen stroma at a greater rate than the comparable groups of corneas stored in equiv-

alent solutions containing bicarbonate. Table 3 shows that the maximum rate of stromal dehydration was observed in the group of corneas stored in bicarbonate-free CPTES. The Tukey-Kramer analysis, comparing the regression coefficients of all groups, shows that the rate of stromal thinning was significantly greater after storage in bicarbonate-free CPTES than after storage for three days in any of the other solutions ($p < 0.01$).

Corneas stored for five days in CPTES also showed a distinctive biphasic curve for the proportional change in stromal thickness during perfusion. Fig. 9 shows that this group of corneas swelled by 100% of their initial thickness during the storage interval and by a further 47% during the initial two hours of perfusion; thereafter these corneas thinned very efficiently at 15.2 (SEM 0.5)% per hour.

Discussion

IONIC COMPOSITION OF THE PRESERVATION SOLUTION

Hypothermic preservation of corneas at refrigerator temperature (4°C) provides the basis of tissue storage for clinical use today. Most storage solutions in popular use are based on a conventional tissue culture medium to provide ionic support for the tissue during the preservation period. These media are specifically designed to maintain the metabolic status of cells during in-vitro incubation at normothermic temperatures. However, it has been suggested that, with the application of hypothermia,

Table 3 Regression coefficients (slopes) of stromal thickness curves and comparisons of the differences between slopes†

Storage solution	Difference between slopes†						Regression coefficient (±SE)‡
	A	B	C	D	E	F	
A. GBR	—	0.66	0.31	1.11*	4.19**	2.97**	-5.26±0.26 n=4
B. CPTES (without Ca ²⁺)	1.10 (1.39)	—	0.34	0.46	3.53**	2.31**	-5.91±0.23 n=4
C. CPTES	1.02 (1.28)	0.96 (1.20)	—	0.80*	3.88**	2.65**	-5.57±0.19 n=5
D. CPTES (+glutathione) (+adenosine)	0.93 (1.16)	0.86 (1.07)	0.74 (0.93)	—	3.08**	1.85**	-6.37±0.13 n=6
E. CPTES (without HCO ₃ ⁻)	0.93 (1.16)	0.86 (1.07)	0.74 (0.93)	0.61 (0.76)	—	1.22*	-9.45±0.13 n=5
F. GBR (without HCO ₃ ⁻)	1.21 (1.51)	1.15 (1.44)	1.07 (1.34)	0.98 (1.23)	0.98 (1.23)	—	-8.22±0.28 n=5
Minimum significant difference†							

†The table is presented as a matrix which allows comparison of the regression data between any two of the experimental groups. The calculated differences between slopes are tabulated in the upper section and these are conveniently compared with the minimum significant difference calculated by the Tukey-Kramer statistical method† and given in the lower section ($p = 0.05$ and values in parentheses $p = 0.01$). Where appropriate differences between slopes that are statistically significant are indicated (* $p < 0.05$ and ** $p < 0.01$).

‡Rate of change of stromal thickness (% per h). Negative values indicate corneal thinning.

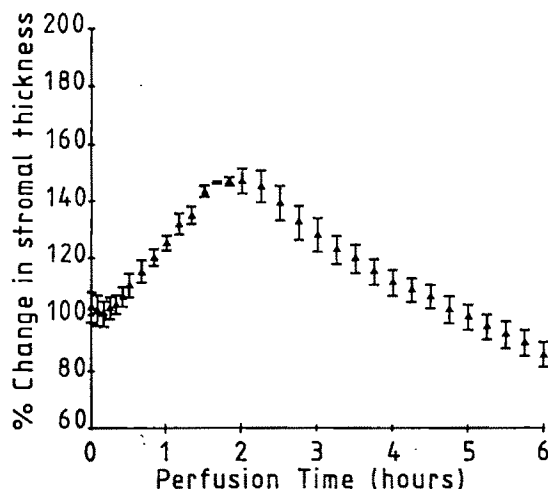


Fig. 9. Stromal hydration changes during normothermic perfusion for a group of corneas after storage in CPTES for five days at 0°C (n=3).

it is unnecessary to support metabolism: control of ion and water distribution between the intracellular and extracellular compartments can be achieved by physical, not biochemical, means. Since the driving force for sodium uptake and potassium depletion is the different ionic balance in extracellular fluid, and since the driving force for net fluid entry is the impermeant intracellular constituents, both changes can be prevented by appropriate alteration to the composition of the extracellular fluid. This is the basis for the design of so-called 'wash-out' solutions used for hypothermic preservation of organs such as kidneys¹ and is also the rationale that we have presented previously for the formulation of CPTES, a hyperkalaemic solution for the preservation of corneas.¹¹

REDUCED CORNEAL SWELLING DURING STORAGE IN CPTES

This study showed that CPTES was more effective than glutathione bicarbonate Ringer's (GBR) solution in restricting stromal swelling during hypothermic storage. Predictably, corneas stored in GBR swelled to the same extent as that reported for tissue stored in the intact eye where the endothelium was bathed throughout with aqueous humour.^{23,24} The effectiveness of CPTES in controlling stromal swelling during storage was shown to be due to the presence of the zwitterionic buffer, TES, since incorporation of an equivalent concentration of TES into the GBR (that is, GBR/TES) produced a similar effect.

BIPHASIC HYDRATION CHANGES DURING PERFUSION

Corneas stored in CPTES showed a characteristic biphasic stromal thickness curve during perfusion which contrasted with the more usual 'temperature reversal' curve shown by the corneas stored in GBR. This again reflects an osmotic response due to the presence of the ampholytic molecule, TES, which permeates into the stroma during storage and establishes an osmotic gradient when the tissue is perfused with GBR. This osmotic gradient, leading to further corneal swelling, was observed to persist consistently for 80-90 min, and presumably reflects the time necessary for complete elution of the TES from the stroma and re-establishment of osmotic equilibrium. Thereafter the presence of an active dehydrating endothelial pump was manifest by a decrease in stromal thickness during the remaining perfusion period. In contrast, the group of corneas perfused with bicarbonate-free medium during this second phase swelled further, thus confirming that endothelial pumping was totally responsible for thinning in those corneas perfused throughout with GBR. Furthermore, the demonstration of reversible swelling during interrupted perfusion with BCFR verified the presence of a bicarbonate-dependent endothelial pump which was responsible for controlling stromal dehydration. The role of TES in generating the initial swelling period was confirmed by repeating the storage experiments with corneas that were subsequently perfused with GBR/TES which contained the same concentration of TES (100 mM) as the storage medium. In these cases the corneas did not swell at the beginning of perfusion but began thinning immediately. Furthermore, corneas stored in GBR/TES and perfused with normal GBR also showed a biphasic curve compatible with that shown by corneas stored in CPTES.

METABOLIC INFLUENCE OF SOME OTHER IONS

While the omission of calcium from CPTES, which has been discussed in a previous publication,¹¹ or the addition of adenosine and glutathione to the CPTES preservation medium did not greatly influence the viability of the endothelium during hypothermic storage, the omission of bicarbonate resulted in more efficient deturgescence of the stored tissue. It has already been explained that during hypothermic storage it is unlikely that normal metabolic support will be required for optimum preservation of corneal endothelium. However, the role of bicarbonate may have special significance for the preservation of this tissue. In studies establishing the role of bicarbonate ions for the function of the electrogenic dehydrating pump of corneal endothelium, Hodson demonstrated a significant benefit from omitting HCO₃ from

corneal bathing solutions.²⁵ He postulated that storage in bicarbonate-free medium prevented the pump from being expended during storage and would therefore prolong the in-vitro life of the tissue. Furthermore, Mayes *et al* also demonstrated the deleterious effect of exogenous bicarbonate on the subsequent functions of rabbit corneal endothelium after prolonged refrigerated storage.²⁶

One consequence of storing tissue in bicarbonate-free medium would be the lack of effective proton-buffering. However, the incorporation of 100 mM TES in CPTES provides efficient pH buffering in the absence of bicarbonate should this prove to be important for improved hypothermic storage of corneas.¹²⁻¹³ TES is one of a family of sulphonic acid derivatives having high solubility and low chemical toxicity which have been used very effectively as biological buffers.^{12-14 27 28} As a pH buffer (for example, in tissue culture applications) these zwitterionic compounds are generally used at a concentration in the range 10-25 mM. However, as described previously,^{11 12} 100 mmol/l TES is included in the preservation solution to act as an impermeant anion during hypothermic preservation, and this concentration of sulphonic acid buffer is known to be tolerated by a variety of cells, tissues and organs.^{11 12 27 29} Garlick *et al*²⁹ discovered a positively beneficial effect of supplementing Krebs-Henseleit buffer solution with 100 mM HEPES (N-2-hydroxyethyl) piperazine-N'-2-ethane sulphonic acid) for the control of acidosis in perfused hearts. They concluded that both the rate and extent of cellular acidification are significantly reduced when 100 mM HEPES was included and also that this concentration of HEPES has a significant protective effect on the ischaemic myocardium.²⁹ In the present study the experiments in which preserved corneas were perfused with GBR/TES showed that corneal endothelium remains metabolically active and fully functional during six hours' perfusion in the presence of 100 mmol/l TES at physiological temperatures. The structural integrity of the endothelium was also confirmed after six hours' perfusion with GBR/TES (Fig. 2C). It is concluded, therefore, that 100 mM TES has no detectable detrimental effects on the structural and functional integrity of corneal endothelium either at normal or at reduced temperature. On the contrary, storage of corneas in the 'intracellular-type' solution, CPTES, was clearly beneficial for restricting stromal swelling during hypothermic storage and yielding corneas that could deturgescere more efficiently than after storage in the 'extracellular-type' solution, GBR.

Further benefits of preventing corneal swelling during hypothermic storage in CPTES are realised by incorporating colloid osmotic agents such as

polyvinylpyrrolidone or chondroitin sulphate, as described elsewhere.^{18 19}

We are grateful to Mr David Chapman, who provided excellent technical help for these studies.

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Hypothermic preservation of corneas in a hyperkalaemic solution (CPTES): II. Extended storage in the presence of chondroitin sulphate

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SUMMARY Periods of preservation for donor corneas, even for short times, are necessary to facilitate optimum conditions in penetrating keratoplasty. However, current techniques for corneal storage at low temperatures may not provide optimal conditions for maintaining tissue integrity. In particular, the ionic composition of the storage medium has received little attention since it has been assumed throughout that the normal complement of ions in tissue culture media will also be suitable for preservation at reduced temperatures. This study extends our previous investigations on the merits of using CPTES (corneal-potassium-TES), a potassium-rich balanced salt solution containing an impermeant anionic pH buffer (TES), as a storage solution specifically designed to prevent the loss of intracellular potassium and minimise endothelial cell swelling during the time that the normal regulatory processes are switched off. The effect of adding the natural polymer chondroitin sulphate (CS) as a colloid osmotic agent to the hyperkalaemic storage medium is now examined. Corneas stored in CPTES containing 2.5% chondroitin sulphate retained a very high level of structural and functional integrity after three, five, and seven days storage at 0°C; furthermore, stromal swelling was restricted to only 21%. All corneas stored in CPTES+2.5% CS showed active endothelial function by thinning efficiently at rates that were greater than those previously reported for rabbit corneas stored for similar lengths of time in either M-K medium or K-sol. The zwitterionic buffers TES and HEPES were interchangeable in the hyperkalaemic solution and were non-toxic to corneal endothelium at a concentration of 100 mM. These compounds offer excellent pH buffering in bicarbonate-free medium.

Attempts to conserve the viability of donor biological tissues *in vitro* during the time interval that is inevitable between harvesting and transplantation rely on two fundamentally different approaches: one is to try to maintain normal physiological function during storage, while the other is to use physical or pharmacological means to depress function in a reversible way, that is to attain a state of 'suspended animation'. Although both are used at present to store corneas for penetrating keratoplasty,^{1,2} preservation by lowering temperature is most widespread, and techniques of cryopreservation offer the only practical means of achieving indefinite storage.^{1,3}

As part of a broader study to improve methods of cryopreservation we have proposed the use of a hyperkalaemic balanced salt solution (CPTES)* to reduce both ionic imbalances and cell swelling during exposure at low temperatures when normal regulating mechanisms are retarded.^{4,5} This solution has been shown to be an effective medium for introducing and removing multimolar concentrations of the cryoprotective agent dimethylsulphoxide.^{4,6}

This type of preservation solution can also provide benefits for intermediate-term storage at reduced temperatures since it is thought that it is unnecessary to support metabolism during hypothermia, and that

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*CPTES: corneal-potassium-TES, a potassium-rich balanced salt solution containing the impermeant biological buffer compound N-Tris (hydroxymethyl)methyl-2-amino ethane sulphonate.

the normal distribution of intracellular water and ions can be controlled physically, rather than biochemically, by appropriate alterations to the composition of the bathing medium.⁷ We have shown that CPTES was effective in maintaining the structural and functional integrity of isolated corneas stored for up to 5 days at 0°C.⁵ Furthermore, CPTES was significantly more efficient than an 'extracellular-type' medium in restricting stromal swelling during the hypothermic storage period. Solutions used routinely in clinical practice for hypothermic storage of isolated corneas are all based on tissue culture medium having an 'extracellular' complement of ions, with the addition of colloid osmotic agents such as dextran, polyvinylpyrrolidone or glycosaminoglycans to help control corneal hydration.¹ The purpose of the present study was to evaluate the effects of adding chondroitin sulphate (CS) as an oncotic agent to the CPTES preservation medium. A comparative study which evaluates the role of polyvinylpyrrolidone (PVP) as the oncotic agent is described elsewhere.⁸

As before, the effects of the hypothermic storage conditions on corneal integrity were assessed by measuring the change of thickness during storage, the ability of the endothelium to control stromal hydration during normothermic perfusion after storage, and by examining endothelial cell morphology and ultrastructure.

Material and methods

Details of the procedures used to isolate and manipulate corneas obtained from New Zealand White rabbits have been described previously.^{4,6} The method of storing isolated corneas in 5 ml of preservation medium at 0°C has also been described.⁵

STORAGE CONDITIONS

Groups of isolated corneas were stored at 0°C in CPTES supplemented with 2.5% (w/v) chondroitin sulphate (Sigma grade III; 99% purity). Chondroitin sulphate was used without further purification. The formulation of CPTES buffer solution has been described in previous communications.^{4,5} The combinations of storage solutions and storage times studied in this investigation are listed in Table 1. Although the effect of refrigerated storage in McCarey-Kaufman medium (M-K medium) has been studied extensively elsewhere,¹ an additional group was included in this study for comparison with the new CPTES storage solution.

M-K medium was prepared as TC199 culture medium with Hanks's salts (Gibco) supplemented with 5% (w/v) dextran-40. (Sigman Chemical Co. Product D-4133) as the oncotic agent.⁹ All storage

Table 1 Storage conditions studied

Storage time at 0°C (days)	Base storage medium	Oncotic agent
5	TC199*	5% Dextran-40*
3	CPTES‡	2.5% CS*
5	CPTES	2.5% CS
7	CPTES	2.5% CS
14†	CPTES	2.5% CS
7	CPHEPES	2.5% CS

*M-K medium. †Examined for morphology only. ‡CPTES= Corneal-potassium-TES.⁵ §Chondroitin sulphate (sodium salt Sigma C.3254. Grade III. 99% pure): 2.5 g added to 100 ml of medium. It was determined by dialysis and atomic adsorption spectrometry that an additional 45 mmols Na⁺ are contributed by incorporating 2.5% CS in the storage media. CPHEPES= Corneal-potassium-HEPES, a potassium rich solution having the same composition as CPTES in which the TES is replaced with 100 mmols/l of the buffer compound HEPES (N-2-hydroxy ethyl piperazine-N'-2-ethane sulphonic acid).

solutions were purged by filtration (Millipore, 0.22 µm) and where appropriate (>3 days' storage) the media were supplemented with 0.1 mg/ml sodium carbenicillin (Pyopen, Beecham Research Laboratories) and 4 µg/ml amphotericin B (Sigma Chemical Co.) as antimicrobial agents. The series of experiments in which corneas were stored in solutions containing CS was carried out without the addition of antibiotics to the storage media. One cornea was held for 14 days in CPTES+2.5% CS without any apparent contamination.

After storage the corneas were either mounted in the perfusion chamber of a specular microscope for monitoring changes in stromal hydration during perfusion at 34°C, or were processed either for optical or for electron microscopy as previously described.^{4,6} During specular microscopy the corneas were normally perfused for a minimum of six hours with glutathione bicarbonate Ringer's solution (GBR); in some cases, however, as previously described,⁵ alternative perfusates were used for either the whole or part of the perfusion period in order to assess specific aspects of corneal function. For example, in some assessments the normal GBR perfusate was changed for a bicarbonate- and carbon-dioxide-free Ringer's solution (BCFR) in order to test the activity of the bicarbonate-dependent metabolic fluid pump in the endothelium.^{1,4,6} The composition of BCFR has been given previously.⁵

To demonstrate the activity of a bicarbonate-dependent endothelial fluid pump, in those individual experiments when the cornea was perfused with GBR/TES as previously described,⁵ it was necessary to use bicarbonate-free Ringer's solution which was also supplemented with 100 mmol/l TES. In this study, therefore, an additional solution (BCFR/TES) was

formulated having the following composition (mmol/l): KCl (4.83); NaCl (30.0); Na_2HPO_4 (4.2); $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$ (0.66); Na_2SO_4 (0.6); MgCl_2 (0.79); CaCl_2 (1.03); NaOH (100.0); HCl (30.0); glucose (4.99); reduced glutathione (1.0) and TES (100.0). The measured osmolality of this solution was 310 mosm.kg⁻¹ and the pH was 7.4 after gassing with a mixture of 93% N_2 and 7% O_2 .

MORPHOLOGY

The gross structural integrity of the endothelial layer was examined by combined staining with trypan blue and alizarin red S (TB/AR).¹⁰ In general this vital staining assay was applied at the end of the storage period; however, in some cases as indicated below, the endothelium was stained after four or six hours' perfusion on the specular microscope. In this way a combined assessment of endothelial structure and function was achieved in the same cornea. Although specular microscopy itself allowed continual examination of endothelial morphology, this was restricted to a small central area, whereas dual staining with TB/AR permitted structural evaluation of the entire endothelial layer.

Ultrastructural examination of endothelial cells in stored corneas was assessed either by transmission electron microscopy (TEM) as previously described,¹¹ or by scanning electron microscopy

(SEM) after critical-point drying from ethanol, and sputter-coating.¹¹

Results

EXTENT OF CORNEAL SWELLING DURING STORAGE

The marked effect of adding a colloid to CPTES solution to prevent stromal swelling during storage at 0°C is illustrated in Fig. 1. The addition of either PVP-360, described elsewhere,⁸ or chondroitin sulphate significantly reduced the extent of swelling during each of the storage intervals. The maximum increase in thickness with either of these colloids was only 27% after one week's storage. In contrast the mean thickness of corneas after five days' storage in either CPTES without added colloids, or in M-K medium, increased by 100% and 55% respectively.

ENDOTHELIAL INTEGRITY AFTER STORAGE IN M-K MEDIUM

Corneas stored in M-K medium for five days increased in thickness by 166 (SEM 4) μm (55%) and maintained this level throughout six hours' perfusion with GBR (Fig. 2). However, morphological examination showed that some damage to the endothelial layer had been sustained during storage. Fig. 3 shows that the integrity of the endothelial layer was compromised after five days' storage and that after seven days a great deal of intracellular disruption was evident on transmission electron microscopy.

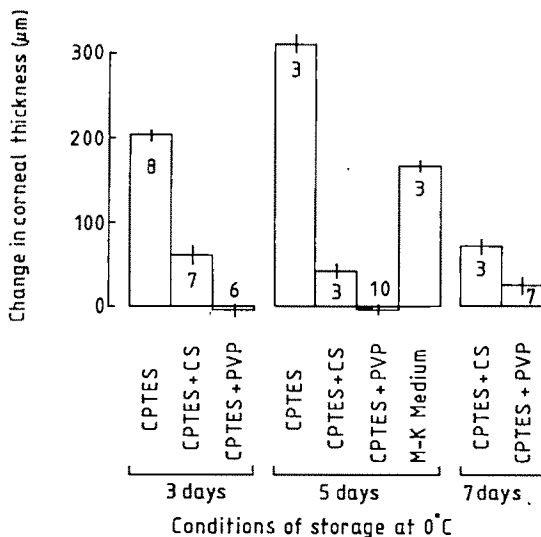


Fig. 1 The effect of polymeric additives in preventing stromal swelling during storage in CPTES at 0°C. Each histogram represents the mean (bar = $\pm$ SEM) change in corneal thickness for the number of corneas indicated in each group. For comparison, data for the changes in corneal thickness during storage in CPTES containing PVP-360 are included from a study published elsewhere.⁸

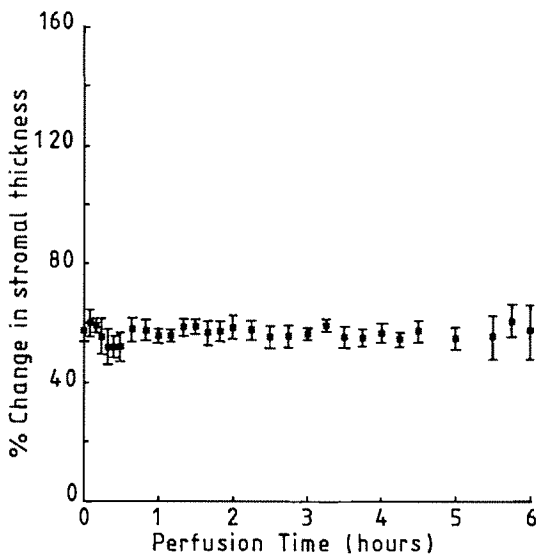


Fig. 2 Mean stromal thickness curves for a group of corneas following storage in M-K medium for five days at 0°C (n=3).

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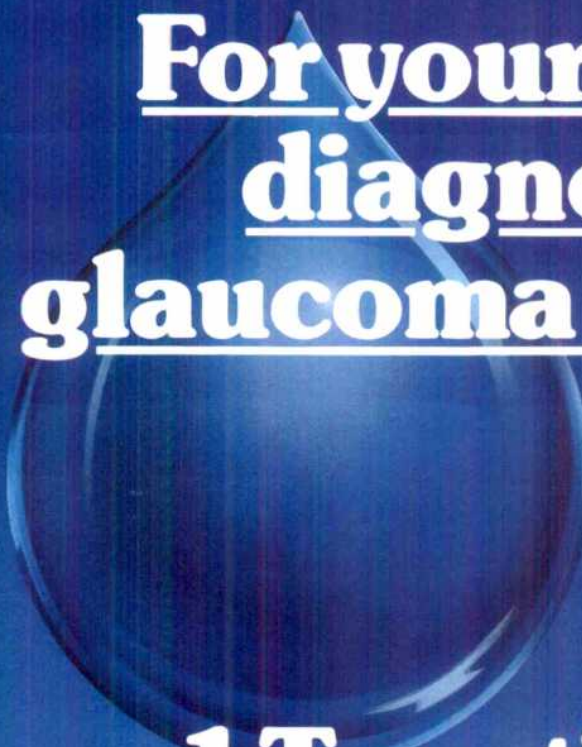
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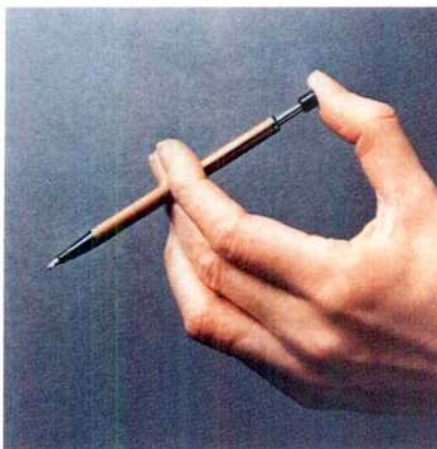
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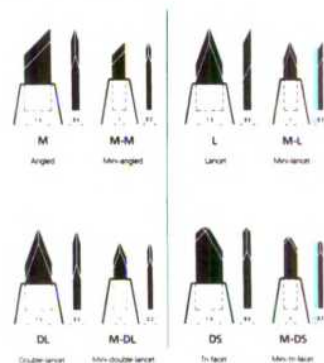
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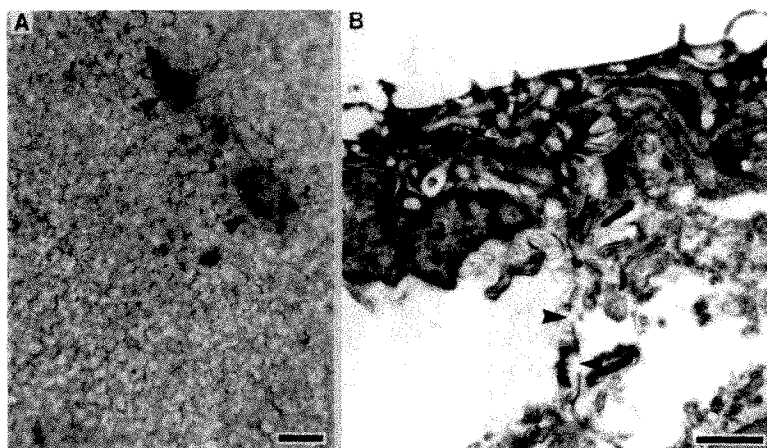


Fig. 3 Endothelial structure after storage in M-K medium at 0°C.

A: Endothelial layer stained with TB/AR after five days' storage showing that areas of the endothelium were disrupted, exposing the underlying basement membrane (arrowed). The remainder of the cell layer appears intact, but the individual cells had a 'rounded' profile instead of the normal angular and polygonal profile; this is probably due to endothelial cell swelling. Scale bar is 100 μ m. B: TEM of endothelium after seven days' storage showing a disrupted endothelial layer with pronounced cytoplasmic swelling and the disruption of posterior and lateral plasma membranes (arrowed). Apical membranes and tight junctions remained intact. Scale bar is 1 μ m.

ENDOTHELIAL INTEGRITY AFTER STORAGE IN CPTES+2.5% CS

Groups of corneas stored for three, five, or seven days in CPTES+2.5% chondroitin sulphate all showed a similar biphasic pattern of stromal

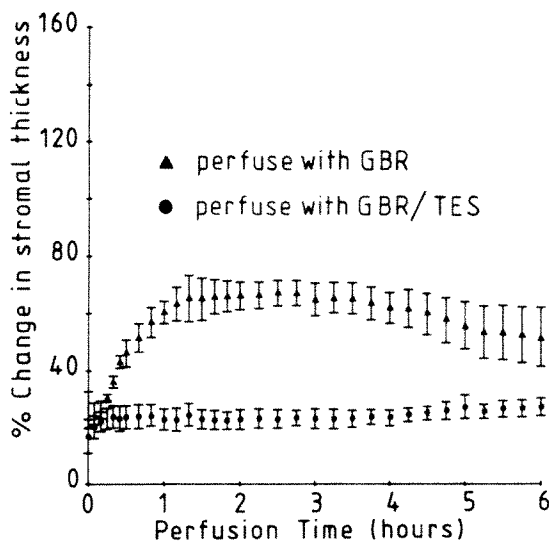


Fig. 4 Stromal thickness curves for groups of corneas stored in CPTES+2.5% CS for three days at 0°C. After storage the corneas were perfused under the specular microscope with either GBR ($\blacktriangle$) or GBR/TES ($\bullet$). The interpretation of these curves which represent the activity of fully functional endothelia is given in the text.

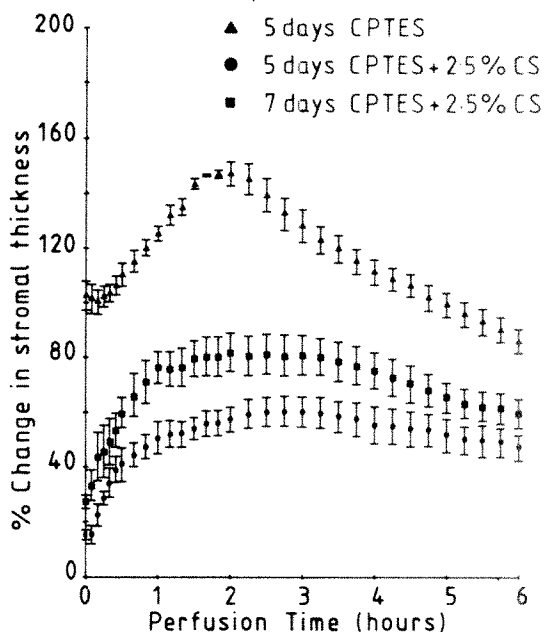


Fig. 5 Biphasic stromal thickness curves for groups of cornea preserved for 5 ($\bullet$) and 7 ($\blacksquare$) days in CPTES+2.5% CS ($n=3$). After the TES was eluted from the stroma during the first phase both groups of corneas thinned during the second phase of perfusion with GBR showing active endothelial function. The mean thickness curve for corneas stored for five days in CPTES without chondroitin sulphate ($\blacktriangle$) is shown for comparison ($n=3$). The lower rate of thinning observed for corneas stored in medium containing CS is probably due to the persistent osmotic gradient established by the retention of exogenous CS in the stroma as explained in the text.

hydration changes during perfusion with GBR (Figs. 4 and 5). Each group of corneas increased in thickness for between one and two hours before the presence of an active dehydrating mechanism was evident. In each group the reversal of stromal swelling during the remainder of the perfusion clearly indicated the presence of a functional endothelium. The rates of stromal deturgescence during the latter part of the perfusion of groups of corneas that had been stored for three, five, or seven days in CPTES+2.5% CS are compared in Table 2.

The osmotic response induced by the presence of TES in the tissue following storage in CPTES medium⁵ was again confirmed in these experiments by perfusing an additional group of corneas with GBR/TES after three days' storage in CPTES+2.5% CS. Fig. 4 shows that the initial period of stromal swelling was abolished when stored corneas were perfused with GBR/TES, and under these circumstances the corneas maintained stromal thickness at a constant level through the perfusion (regression slope=0.1 (standard error 0.1)%/h).

The functional viability of the endothelial layer in a cornea stored in CPTES+2.5% CS for three days and then perfused with GBR/TES was further demonstrated by reversible swelling of the stroma when the metabolic pump was inactivated during perfusion. Fig. 6 again shows that the presence of 100 mmol/l TES in the GBR perfusate prevents the initial swelling normally observed in corneas perfused with GBR without TES and that inhibition of the active bicarbonate-dependent pump, leading to stromal swelling, was achieved by substituting the GBR/TES perfusate with BCFR/TES. The reactivation of the endothelial pump and corneal thinning was also demonstrated by reverting to perfusion with GBR/TES.

Comparing this response, however, with that of the paired cornea which was stored in CPTES without chondroitin sulphate for the same length of time, we found the rates of change of stromal

thickness during the periods of perfusion with both GBR/TES and BCFR/TES to be noticeably different. Fig. 6 shows that the swelling and thinning rates (regression slope (standard error)) for the cornea stored in CPTES+2.5% CS were 33 (1) and 6 (2) $\mu\text{m}/\text{h}$ respectively compared with the swelling and deturgescence rate of 25 (1) $\mu\text{m}/\text{h}$ for the cornea stored in CPTES alone. The implication of these data, that storage in medium containing chondroitin sulphate in some way influences the subsequent rate of change of hydration under the influence of a functioning endothelium is discussed below. The curves in Fig. 6 also demonstrate that the endothelium in the preserved corneas remains fully functional during a further eight hours' normothermic perfusion in the presence of 100 mM TES, confirming the nontoxicity of the TES buffer.

The microscopic appearance of the endothelial layer in corneas stored in CPTES+2.5% CS for three, five, and seven days is shown in Figs. 7-9 respectively. It is clearly apparent that in all cases the

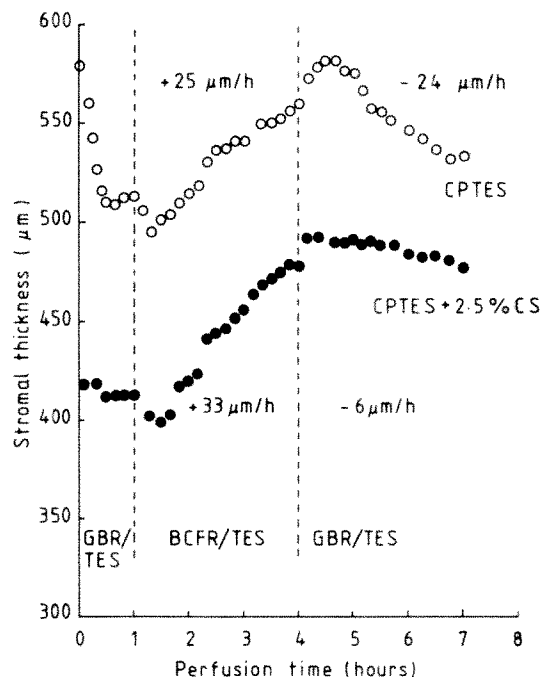


Fig. 6 Stromal thickness curves demonstrating fully functional endothelia in a pair of corneas preserved for three days at 0°C in either CPTES (○) or CPTES+2.5% CS (●). Stromal swelling and thinning rates are indicated for the periods during which the endothelial pump is switched off and then reactivated during normothermic perfusion with either BCFR/TES or GBR/TES respectively. See text for further discussion of these curves.

Table 2 Stromal thinning in corneas preserved in CPTES+2.5% chondroitin sulphate at 0°C.

Storage time (days)	Mean initial thickness* in $\mu\text{m}/\text{h}$ (SEM)	Rate of thinning	
		%/h (SEM)	μm
3	283 (12)	5.2 (0.3)	14.7
5	288 (7)	4.4 (0.1)	12.7
7	261 (7)	7.8 (0.3)	20.3

*Thickness of cornea measured within 60 min of enucleation; this is the value to which all subsequent changes in thickness are normalised.

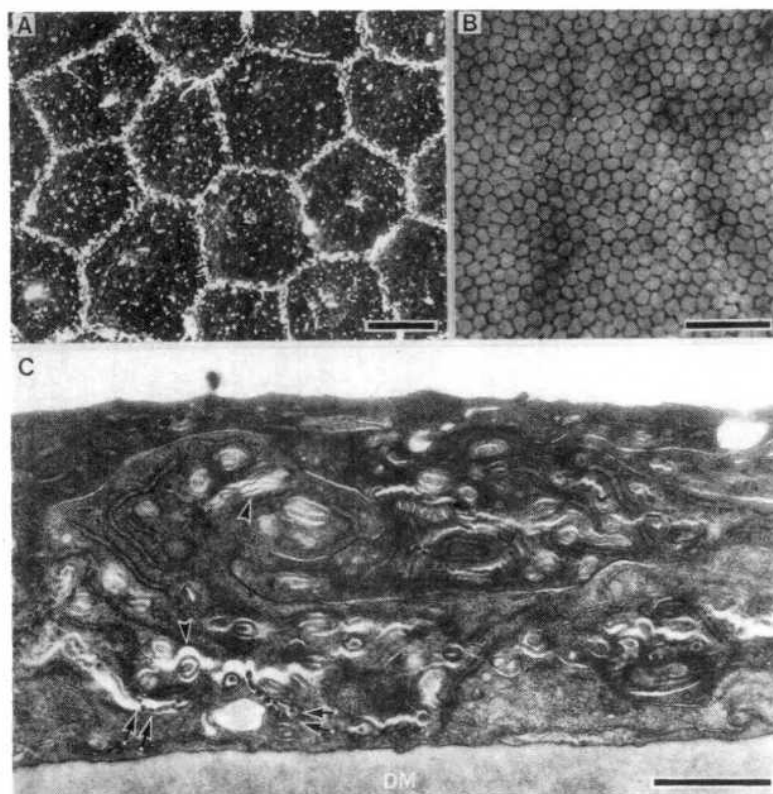


Fig. 7 Corneal endothelium after three days' storage at 0°C in CPTES+2.5% chondroitin sulphate. A: SEM of intact endothelial layer immediately following the storage period. The cells show only slight lifting of the apical flaps and a nearly normal complement of microvillae. B: TB/AR staining showing a nearly normal endothelial cell layer with no loss of cells and no uptake of trypan blue. C: TEM shows an intact, normal endothelial layer closely apposed to Descemet's membrane (DM), only slight swelling of the mitochondrial outer compartment (arrowheads) and the presence of beaded forms with swollen cristae (double arrows) is apparent. Scale bar: A: 10 µm; B: 100 µm; C: 1 µm.

endothelial mosaic is well preserved, and Fig. 10 shows that even after 14 days' storage very little damage was detectable. Scanning electron microscopy confirmed that an intact cell layer was present at the end of each storage period and that damaged cells were confined to areas of the cell layer in the vicinity of ridges or folds. Transmission electron microscopy showed near normal endothelial ultra-structure after three days' storage, with only slight mitochondrial swelling apparent. As storage time increased, further changes occurred to the endothelium: though a few cells showed increased Golgi activity and a proliferation of the apical cytoplasm and there was some slight intracellular oedema, most cells had only modest and reversible structural changes even after seven days' storage.

Replacement of TES in the hyperkalaemic solution with an alternative zwitterionic buffer (100 mmol/l HEPES; Table 1) also resulted in excellent preservation of corneal structure and function after seven days' storage at 0°C. Fig. 11 shows the presence of an active fluid pump in the endothelium of a cornea stored for seven days in CPHEPES+2.5% CS. This cornea also had a morphologically intact endothelial

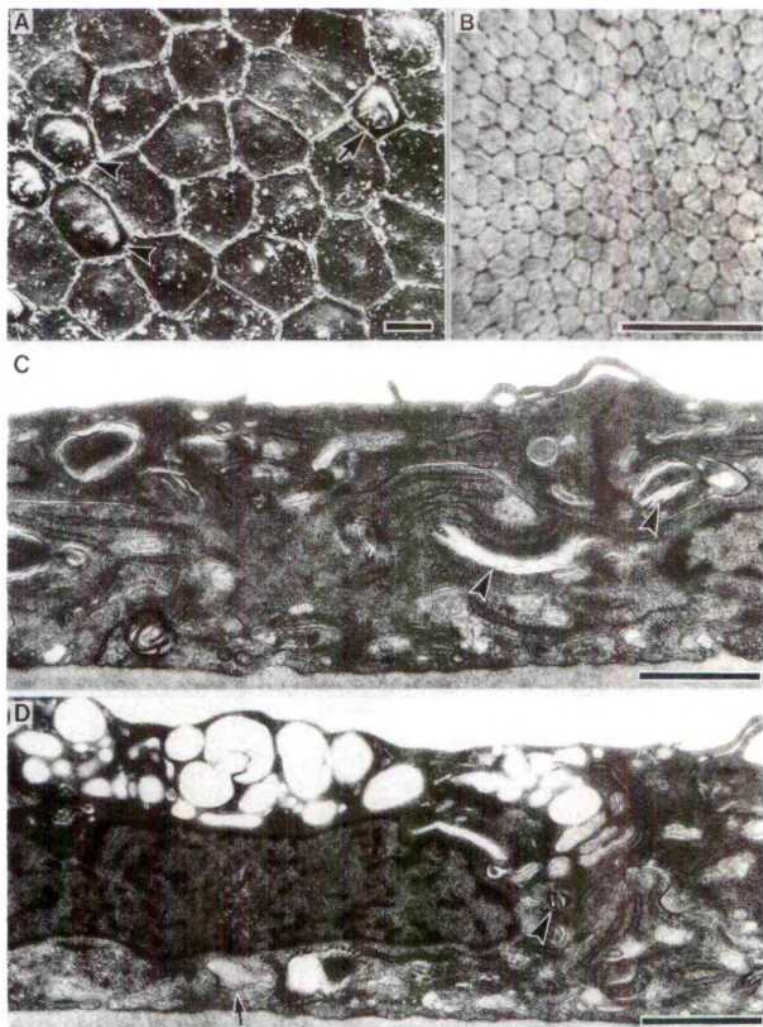
layer at the end of the storage and perfusion period (Fig. 10).

Discussion

The rationale for using a potassium-rich solution containing an impermeant anion with good hydrogen ion buffering for hypothermic preservation of corneas has been described at the beginning of this report and in previous publications.^{4,5} Moreover, it has been shown that isolated corneas are better preserved at 0°C in the 'intracellular-type' solution, CPTES, than in the 'extracellular-type' solution GBR.⁵ Further studies have now been undertaken to assess the value of adding colloid osmotic agents to the hyperkalaemic storage medium.

In the present study the survival of corneal endothelium after storage in CPTES solution containing the natural polymer chondroitin sulphate is assessed for comparison with a parallel study that evaluated the merits of polyvinylpyrrolidone (PVP) as an oncotic agent.⁶ Chondroitin sulphate has been used in recent years as an ingredient of other corneal storage solutions.¹²⁻¹⁴

Fig. 8 Corneal endothelium after five days' storage at 0°C in CPTES+2.5% CS. A: SEM shows an intact cell layer with evidence of active cellular ingrowth (rosette formation – arrow). Many cells had a 'cobblestone'-like appearance, with a central bulge (arrowheads). Apical flaps were swollen. B: Good preservation of the endothelial mosaic as delineated by staining with alizarin red S. No cells stained with trypan blue. C and D: TEM immediately following storage. The endothelium remains nearly normal. Apical flaps are raised but tight junctions remain closed. There is more pronounced mitochondrial swelling in places (C, arrowheads) and the appearance of some condensed forms (D, arrowhead); smooth endoplasmic reticulum is swollen (D arrow). In some areas there is a supranuclear proliferation of vesicles which may correlate with the bulges seen in the SEM. Scale bar A: 10 µm; B: 100 µm; C, D: 1 µm.



ADDITION OF ONCOTIC AGENTS TO CORNEAL STORAGE MEDIA

A variety of oncotc agents have been used to supplement corneal storage solutions and effectively restrict stromal swelling during hypothermic preservation.¹ Polyvinylpyrrolidone (PVP) has had only limited use as a colloid in hypothermic storage solutions for corneal preservation at refrigerator temperatures,¹⁵ and we have recently reported elsewhere⁸ that PVP-360 (average molecular weight 360 000 daltons) is extremely effective in preventing any stromal swelling in corneas stored at 0°C for up to five days and restricts swelling to less than 10% of the original thickness in those corneas stored for up to seven days. However, even though the gross struc-

tural integrity of the endothelial layer was apparently well preserved, corneas stored for longer than three days in CPTES containing 7% PVP-360 did not retain good endothelial function, and the endothelial ultrastructure revealed a number of detrimental changes; these were probably related to the pinocytotic uptake of the polymer.⁸

Dextran has also been used as a colloid osmotic agent in corneal preservation solutions,^{9,16} but as shown in this study it is clearly not as effective in restricting stromal swelling as PVP-360 or chondroitin sulphate. Endothelial function was better preserved after storage for five days in M-K medium containing dextran-40 than in CPTES containing PVP-360,⁸ but a number of detrimental structural changes were

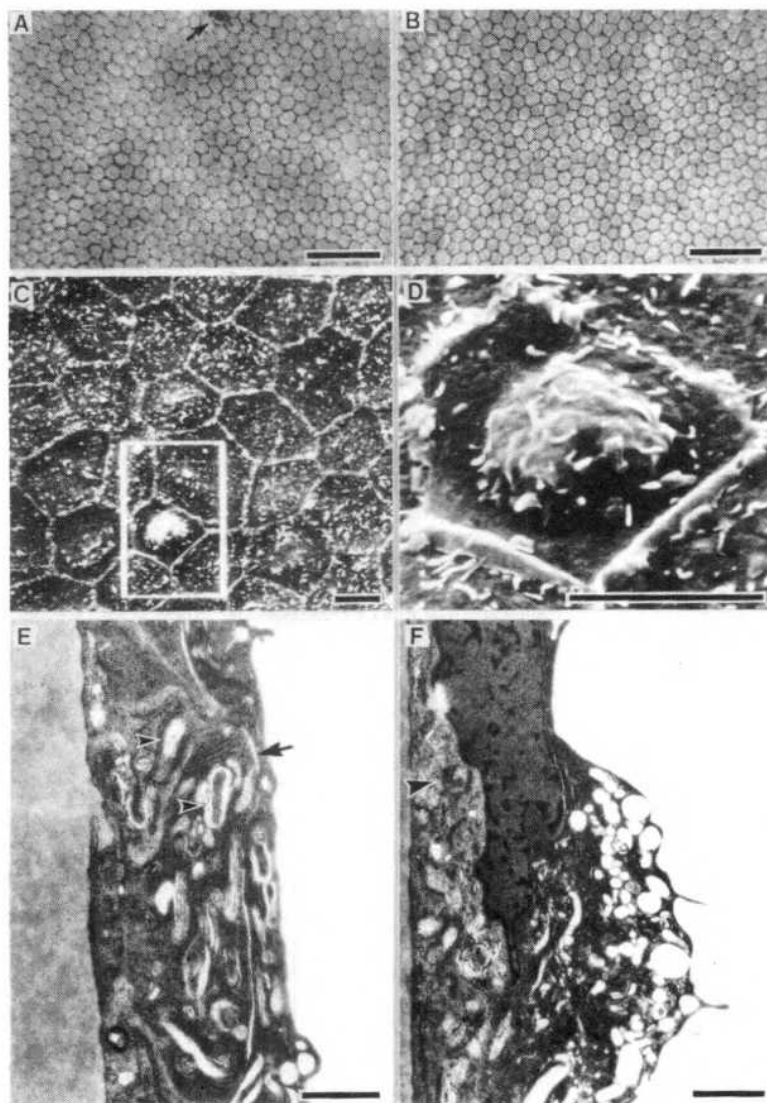


Fig. 9 Corneal endothelium after seven days' storage in CPTES + 2.5% chondroitin sulphate. A: Excellent endothelial morphology revealed by TB/AR staining immediately after seven days' preservation. Only a single cell had become permeable to trypan blue (arrow). B: Complete endothelial layer integrity was retained after rewarming to 34°C and perfusion under the specular microscope for 4 h during the functional assessment shown in Fig. 5. C: SEM of endothelial layer; note increased number of microvillae. D: Higher magnification of area outlined in C showing cellular protrusion with numerous blebs and microvillae. E: TEM showing continued maintenance of nearly normal morphology with slight widening of intercellular space (arrow) and altered mitochondria (arrowheads). F: Area of vesicular proliferation related to increased Golgi activity, which may correlate with the cellular protrusions seen by SEM; note slight basal oedema (arrowhead). Scale bar: A, B: 100 µm; C, D: 10 µm; E, F: 1 µm.

nevertheless observed after five and seven days' storage. Recent reports by other workers using human corneas also show structural damage in corneas rewarmed to 37°C after storage in M-K medium for up to six days.¹⁷

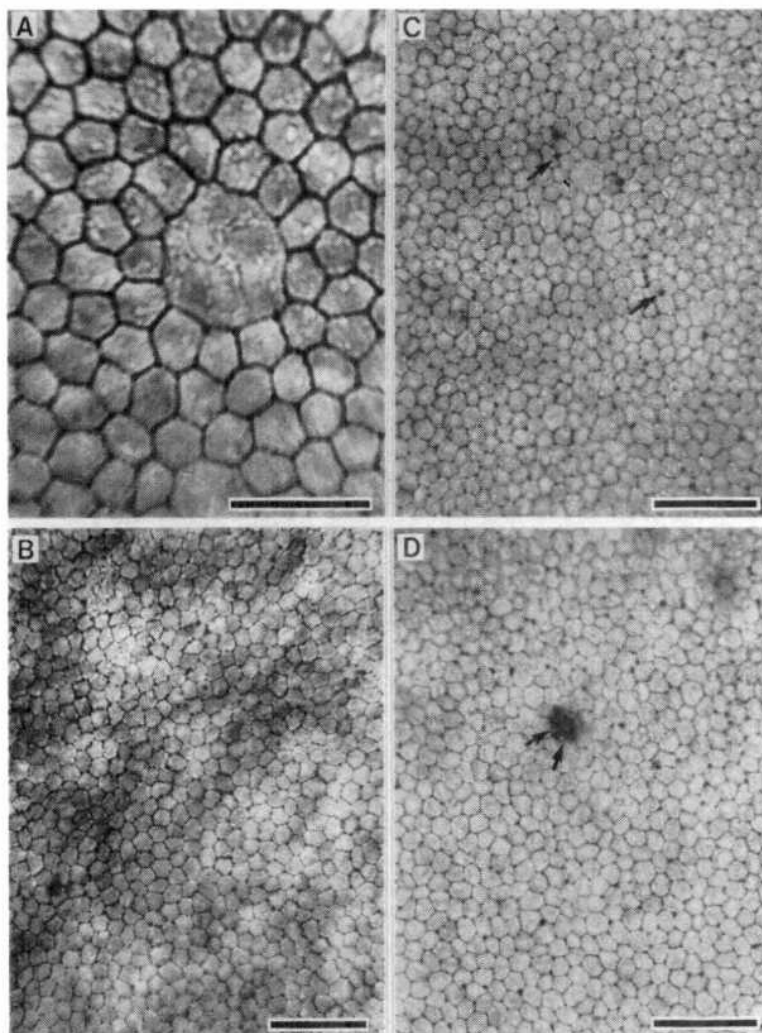
SUPERIORITY OF CHONDROITIN SULPHATE

The most striking observation in this study was the superior quality of corneas stored in CPTES containing 2.5% (w/v) chondroitin sulphate after any of the storage periods. Chondroitin sulphate, which is a negatively charged glycosaminoglycan with an average molecular weight of approximately 40 000

daltons (range 25 000-80 000), was very effective in helping to maintain stromal hydration during hypothermic storage and, as with storage in CPTES + PVP-360,⁸ corneas were thin and perfectly transparent at the end of storage. However, in contrast to corneas stored in CPTES + PVP-360 those stored at 0°C in CPTES with 2.5% CS also retained a fully functional endothelium, as indicated by stromal thinning during subsequent perfusion on the specular microscope.

The functional ability of corneas stored in CPTES + 2.5% CS was further demonstrated by the reversible swelling induced by inhibiting and then

Fig. 10 Structural integrity of corneal endothelium after seven and 14 days' storage in hyperkalaemic preservation solutions containing chondroitin sulphate. A: Seven days' storage in CPTES+2.5% CS. The entire endothelial layer was intact and all cells were viable by trypan blue exclusion. A few giant multinucleate cells were observed as shown here. B: Seven days' storage in CPHEPES+2.5% CS showing a normal mosaic of endothelial cells covering the entire corneal button. C: Fourteen days' storage in CPTES+2.5% CS. The cell layer was intact and sites of individual cell replacement were apparent (arrows). Occasional enlarged cells were also observed. D: Fourteen days' preservation in CPTES+2.5% CS showing that only minor injury was sustained during storage under these conditions; a few single cells are lost from the endothelial layer and replaced by neighbouring healthy cells (arrow). Scale bar is 100 μm .



reactivating the bicarbonate-dependent pump of the endothelium. It was noted, however, that the rates of swelling when the pump was switched off was greater, and the rate of thinning after reactivation was less, than the values recorded for the paired cornea stored for the same length of time in CPTES without chondroitin sulphate. Furthermore, the mean rate of thinning during perfusion for groups of corneas stored in CPTES+2.5% CS for five days was less than for a comparable group stored in CPTES without chondroitin sulphate (see Fig. 5).⁵ These observations are consistent with those previously reported by Hull *et al.*, who noted that rabbit corneas stored at +4°C in K-sol containing 2.5% CS failed to 'temperature reverse'; in contrast corneas stored in

M-K medium thinned at 6 or 9 $\mu\text{m/h}$ after storage for three and seven days respectively.¹² They postulated that the shorter chain length moieties of chondroitin sulphate penetrate the stroma more rapidly than the longer chain length molecules, giving rise to an increased osmotic force across the endothelium. In our experiments this would account for the higher rate of swelling in corneas whose bicarbonate pump was switched off during perfusion following storage in CPTES+2.5% CS. Moreover, it is proposed that, because chondroitin sulphate is a natural glycosaminoglycan, normally present in corneal stroma, exogenous chondroitin sulphate may be sequestered in the stroma and eluted more slowly than foreign polymers such as dextran following

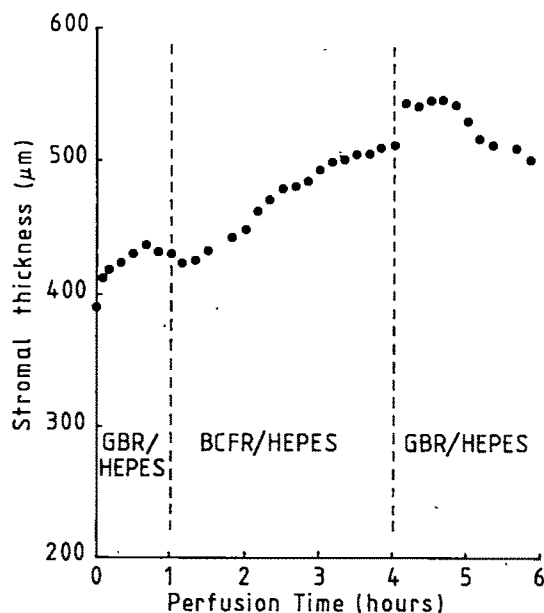


Fig. 11 Functional viability of a cornea preserved for seven days in CPHEPES+2.5% chondroitin sulphate at 0°C. Reversible swelling of the stroma is demonstrated by alternate perfusion in GBR/HEPES and BCFR/HEPES, which enables the endothelial bicarbonate-dependent pump to be switched off and reactivated as described in the text. This physiological test was conducted at 34°C in the presence of 100 mmol/l HEPES, showing the non-toxicity of this buffer compound.

storage. A persistent osmotic gradient would therefore be established across the endothelium of corneas stored in CPTES+CS resulting in the lower rates of thinning observed during subsequent perfusion with GBR or GBR/TES compared with corneas stored in CPTES alone.

On this basis the profile of the stromal swelling curves for groups of corneas stored for three, five, or seven days in CPTES+2.5% CS (Figs. 4 and 5) might be explained in the following way. Initially corneas are thin, having swollen by less than 20% during storage. The stroma then swells during the first one to two hours of perfusion owing to the osmotic gradient established by the presence of both TES and exogenous chondroitin sulphate which have permeated the stroma during storage. TES will be eluted more rapidly (within 80-90 min as shown previously⁵) than chondroitin sulphate, which is probably bound in some way, resulting in a persistent osmotic gradient which increases the rate of passive permeation of water counteracting the active dehydrating mechanism of the functioning endothelium. After elution of the TES all corneas stored

in CPTES+2.5% CS showed an active thinning of the stroma during the latter part of the perfusion, and the rates of thinning were greater than those previously reported for rabbit corneas stored for similar lengths of time in either M-K medium or K-sol.¹²

The use of glycosaminoglycans in corneal storage solutions was proposed over 20 years ago by groups of Japanese workers who reported successful preservation for 1 week.¹ More recently a number of experimental and clinical reports have advocated or supported the inclusion of chondroitin sulphate in both low temperature preservation solutions such as K-sol^{12-14 16 18} and organ culture media for storage at 37°C.^{19 20} The present study confirms the superiority of chondroitin sulphate as a non-toxic colloid osmotic agent for restricting stromal swelling and for maintaining endothelial cell structure and function during refrigerated storage. Moreover, these experiments support our previous proposal that during hypothermic storage it is unnecessary to support metabolism by bathing corneas in solutions based on tissue culture media and that optimum maintenance of the ionic and hydraulic balance within corneal endothelium is more likely to be achieved at reduced temperatures by using an 'intracellular' type solution such as CPTES.¹⁵

Additional benefits such as the superior pH buffering capacity of CPTES and CPHEPES remains to be evaluated in further studies.^{21 22} However, it is well known that the structure and physiological function of corneal endothelium is sensitive to the ambient pH.²³⁻²⁷ The control of pH during tissue storage is therefore, extremely important for optimum preservation, and, although this particular aspect of corneal preservation has received little attention, it has been reported that pH is better controlled in some corneal storage solutions than in others.^{28 29} The presence of 100 mmol/l of a zwitterionic buffer such as TES or HEPES in this hyperkalaemic preservation medium means that their hydrogen-ion buffering capacity in the physiological range will be better than any other corneal storage or irrigating solution, and, as discussed in our previous communication,⁴ the role of changes in pH, especially in bicarbonate-free medium, demands further study.

Technical support for these experiments was provided by Mr David Chapman, whose care and skills we acknowledge with gratitude.

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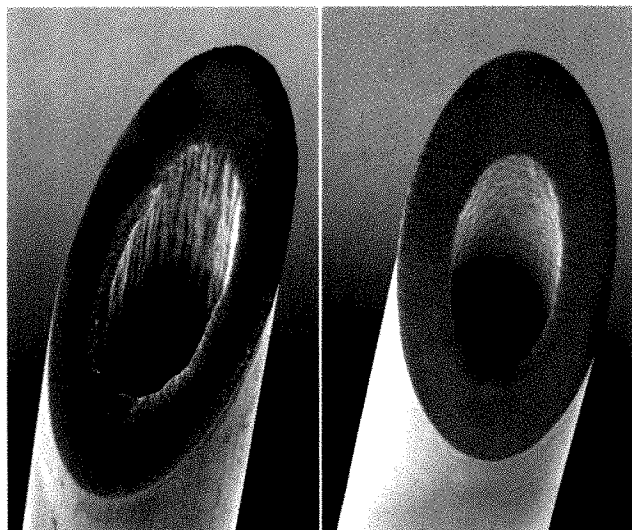
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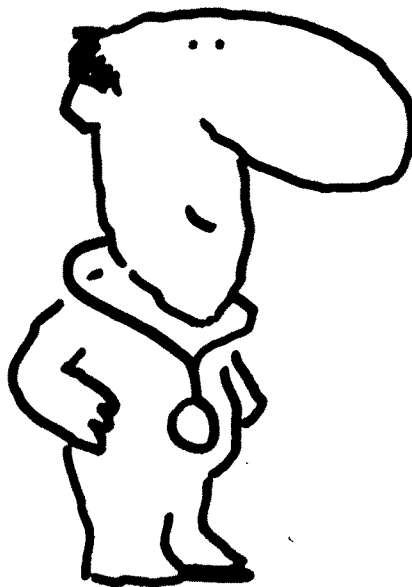
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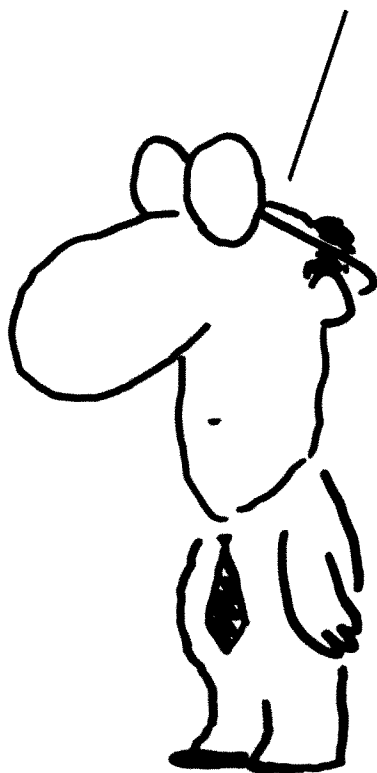
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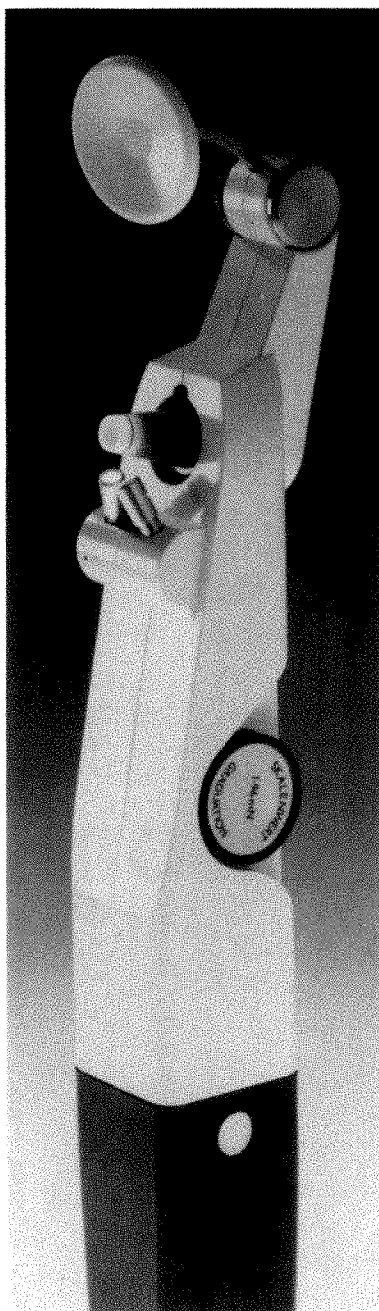
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Endothelial cell damage in human and rabbit corneas stored in K-Sol without antioxidants

T SANJEEVA REDDY, EMILY D VARNELL, ROGER W BEUERMAN, NICOLAS G BAZAN, AND HERBERT E KAUFMAN

From the Lions Eye Research Laboratories, LSU Eye Center, Louisiana State University Medical Center School of Medicine, New Orleans, LA 70112, USA

SUMMARY Human and rabbit corneas were stored at 4°C in K-Sol with and without antioxidants (ascorbic acid, reduced glutathione, α -tocopherol, and retinol acetate) for two to three weeks. All the corneas were then examined visually and by scanning electron microscopy. They appeared clear and slightly oedematous. Scanning electron micrographs were used to grade corneal endothelial cell morphology in a masked manner in terms of cell shape, cell borders, cell swelling, and apical holes. Corneas stored in K-Sol without antioxidants showed changes in cell shape, cell borders, and apical holes. Human corneas showed more morphological changes than rabbit corneas. The results suggest that antioxidants in K-Sol have an important role in the preservation of endothelial cell morphology.

K-Sol corneal preservation medium allows better long-term storage of corneas than storage in McCarey-Kaufman (M-K) medium.¹⁻⁴ Chondroitin sulphate, the major component of K-Sol, acts as an antioxidant⁵ apart from its role in maintaining osmolality. Lipid peroxides are known to cause considerable damage to membranes by altering their structural and functional components.⁶ Since the maintenance of endothelial cell viability is the most important consideration in long-term preservation of

corneas, we have undertaken the present studies to understand the effect of antioxidants in K-Sol on the morphology of endothelial cells.⁷

Materials and methods

K-Sol corneal preservation medium was prepared as described previously^{3,4} or obtained from Cilco, Inc. (Bellevue, Washington). The quantities of antioxidants in K-Sol were as follows: ascorbic acid, 0.28 μ M; α -tocopherol phosphate, 0.02 μ M; vitamin A acetate, 0.43 μ M, and reduced glutathione, 0.16 μ M. K-Sol without antioxidants was prepared

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Table 1 *Details of human corneas stored in K-Sol*

Age (years)	Cause of death	Time of enucleation	Eye	Days stored in K-Sol with antioxidants	Days stored in K-Sol without antioxidants	Visual appearance
85	Vascular insufficiency	2 hr 45 min	OD	18	—	Clear and slightly oedematous
			OS	3*	15	
80	Acute renal failure	1 hr	OD	4*	14	Clear and slightly oedematous
			OS	18	—	
69	Renal failure	2 hr 15 min	OD	16	—	Clear and slightly oedematous
			OS	2*	14	
72	Respiratory arrest	11 hr 52 min	OD	4*	14	Clear and slightly oedematous
			OS	18	—	
40	Malignant melanoma	2 hr 50 min	OD	17	—	Clear and slightly oedematous
			OS	3*	14	

*Received from eye bank in standard K-Sol (with antioxidants) and then transferred to K-Sol without antioxidants in our laboratory.

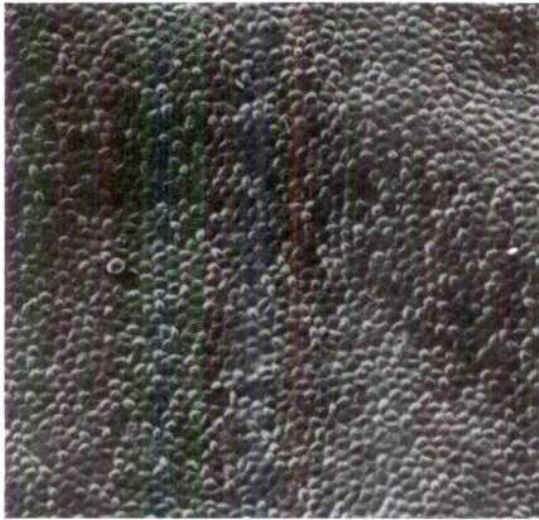


Fig. 1A

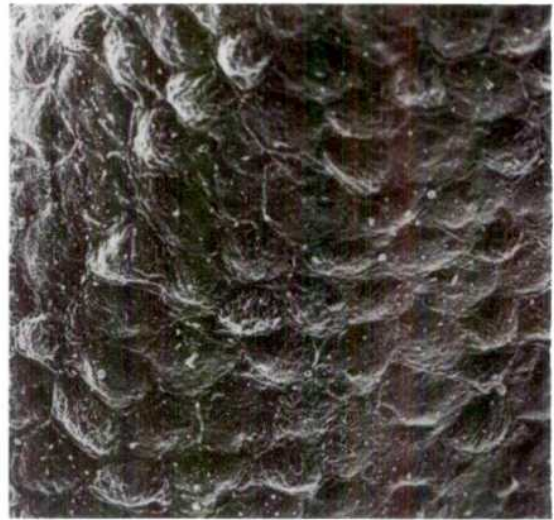


Fig. 1B

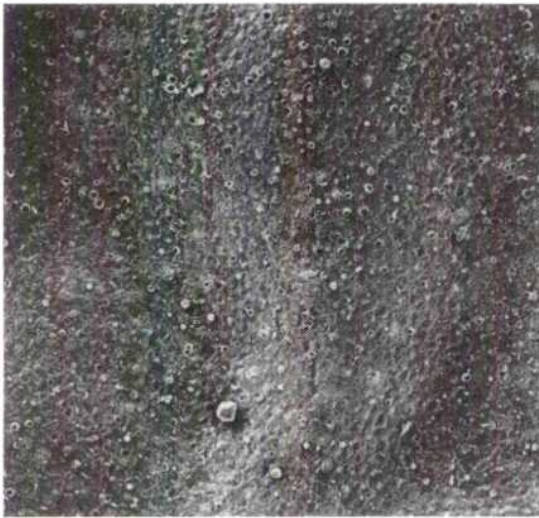


Fig. 1C



Fig. 1D

Fig. 1 Rabbit corneal endothelial cells after 14 days of storage in K-Sol. Corneas stored in K-Sol with (A and B) and without (C and D) antioxidants (α -tocopherol, ascorbic acid, retinol acetate, and reduced glutathione). (Scanning electron microscopy; A and C, $\times 160$; B and D, $\times 800$).

from custom-made medium 199 without ascorbic acid, α -tocopherol, retinol acetate, or reduced glutathione (Gibco Laboratories, Grand Island, New York).

Six New Zealand white rabbits weighing 4 to 6 kg each were used. The rabbits were killed by an overdose of pentobarbital. The eyes were enucleated and washed with normal saline. Corneas with a narrow scleral rim were obtained. The time between

the death of the rabbits and the use of the corneas did not exceed 2 hours. The corneas were washed with balanced salt solution and then transferred into K-Sol. One cornea from each rabbit was stored at 4°C in K-Sol with antioxidants and the other cornea in K-Sol without antioxidants. Four corneas from each group were removed after 14 days of storage, washed with balanced salt solution, examined visually, and processed for scanning electron microscopy. The

Table 2 Morphological characteristics of endothelium of corneas stored in K-Sol

Species	Days of storage	n	Antioxidants	Cell shape	Cell borders	Cell swelling	Apical holes	Total morphological grade
Human	16-18	5	+	1.88 (0.13)	1.50 (0.00)	1.50±0.00	1.75 (0.14)	1.66 (0.06)
	14-15	5	-	2.63 (0.13)*	3.00 (0.20)*	1.50±0.00	3.50 (0.20)*	2.66 (0.09)*
Rabbit	14	4	+	1.50 (0.20)	1.50 (0.00)	1.50±0.29	1.50 (0.20)	1.50 (0.16)
	14	4	-	1.83 (0.17)	2.00 (0.00)*	1.67±0.17	3.33 (0.17)*	2.21 (0.11)*
Rabbit	21	2	+	2.00	2.00	2.00	2.50	2.13
	21	2	-	3.00	3.00	2.00	3.50	2.88

Morphological characteristics of endothelial cells of corneas stored in K-Sol were graded from 1 to 4 using scanning electron micrographs taken from centre of the cornea. Values are mean with standard error of the mean in parentheses. The details of grading are explained in the 'Methods and materials' section. Values marked with asterisks are significantly different from values obtained for corneas stored in K-Sol with antioxidants ($p < 0.01$ by Student's *t* test).

remaining corneas were processed similarly after 21 days of storage.

Five pairs of human corneas were obtained from different eye banks round the country (Table 1). The human corneas had been stored in K-Sol (with antioxidants) by the eye banks for two to four days for preservation during transport. On arrival at the Eye Center the corneas were washed with balanced salt solution. One cornea from each pair was stored in K-Sol with antioxidants and one in K-Sol without antioxidants. The corneas were removed from storage after 14 to 15 days, washed, examined visually, and processed for scanning electron microscopy.

For scanning electron microscopy the corneas removed from K-Sol medium were washed with balanced salt solution and transferred into fixative solution (1% paraformaldehyde and 2.5% glutaraldehyde in 0.1 M sodium cacodylate buffer, pH 7.4) and stored at 4°C for 3 hours. After further dissection the fixed corneas were incubated in an isotonic buffer solution (0.1 M sodium cacodylate buffer, 0.5% sucrose) overnight at 4°C. After postfixation in 1% osmium tetroxide in 0.1 M sodium cacodylate buffer (pH 7.4) and ethanolic dehydration, the specimens were further processed for scanning electron microscopy.²

Corneal endothelial cell damage was quantified in a masked fashion from scanning electron micrographs of the centre of the cornea at magnifications of $\times 200$, $\times 500$ and $\times 1000$. A scoring system was used for grading cell shape, cell borders, cell swelling, and apical holes in the cell. Cell shape was graded from 1 (normal hexagonal shape) to 4 (irregular pleomorphic cells). Cell borders were graded from 1 (borders with no irregularities and interdigitations) to 4 (irregular borders with prominent interdigitations). Cell swelling was graded from 1 (flat cells without swelling) to 4 (marked swelling). Apical holes on the endothelial cell surface were graded

from 1 to 4: 1, 0% holes; 2, 10–20% holes; 3, 40–50% holes; and 4, 70–100% holes. The mean of the sum of all these measurements was termed the total morphological grade.

Results

Human and rabbit corneas stored in K-Sol with and without antioxidants for 14 to 21 days were clear but slightly oedematous on visual examination. Rabbit corneas stored in K-Sol without antioxidants for 14 days showed significantly higher numbers of endothelial cell apical holes than corneas stored in K-Sol with antioxidants, as shown by scanning electron micrographs (Fig. 1, Table 2). When the storage was prolonged to 21 days, endothelial cell shape and cell borders were more significantly distorted and apical holes were more numerous in corneas stored in K-Sol without antioxidants than in corneas stored in K-Sol with antioxidants (Fig. 2, Table 2).

Human corneas stored for a total of 16 to 18 days (including transportation time) in K-Sol with antioxidants showed only minor changes in endothelial cell shape, cell borders, swelling, and apical holes (Fig. 3, Table 2). In contrast, human corneas stored for two to four days in K-Sol with antioxidants (during transportation by the Eye Bank), followed by 14 to 15 days in K-Sol without antioxidants in our laboratory, showed significant changes in endothelial cell shape, cell borders, and apical holes (Fig. 3, Table 2).

Discussion

The present investigation shows that the lack of antioxidants (ascorbic acid, α -tocopherol, retinol acetate, and reduced glutathione) in K-Sol results in considerable damage to the endothelial cells. The damage seems to be greater in human corneas than in

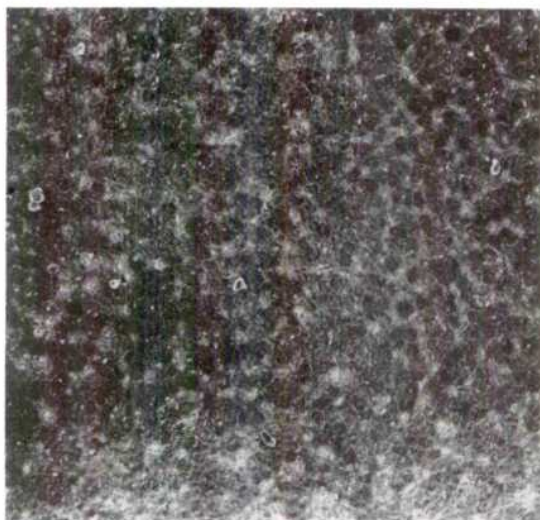


Fig. 2A



Fig. 2B

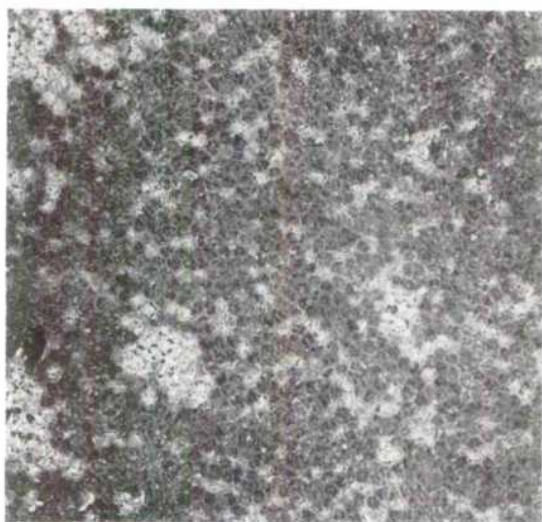


Fig. 2C



Fig. 2D

Fig. 2 Rabbit corneal endothelial cells after 21 days of storage in K-Sol. A and B: corneas stored in K-Sol with antioxidants. C and D: corneas stored in K-Sol without antioxidants. Scanning electron microscopy: A and C, $\times 160$; B and D, $\times 800$.

rabbit corneas. The amount of damage may depend on the levels of antioxidants in individual corneas and the presence of various ions and other metabolites that increase or decrease lipid peroxidation. The levels of antioxidants in K-Sol (α -tocopherol, $0.02 \mu\text{M}$; retinol acetate, $0.43 \mu\text{M}$; ascorbic acid, $0.28 \mu\text{M}$; and reduced glutathione, $0.16 \mu\text{M}$) are low. Recent studies indicate that the concentrations of ascorbic acid⁸ and α -tocopherol⁹ required to cause

significant inhibition of arachidonic acid oxidation range from 10^{-3} to 10^{-4} M. Further, the chemical and metabolic fate of added antioxidants in the medium, which may influence the viability of corneal endothelium, is not yet clear. For example, Edelhauser and others¹⁰ reported that the ratio of oxidised to reduced glutathione in K-Sol is important in maintaining endothelial cell structure and function. Although the levels of glutathione in M-K medium

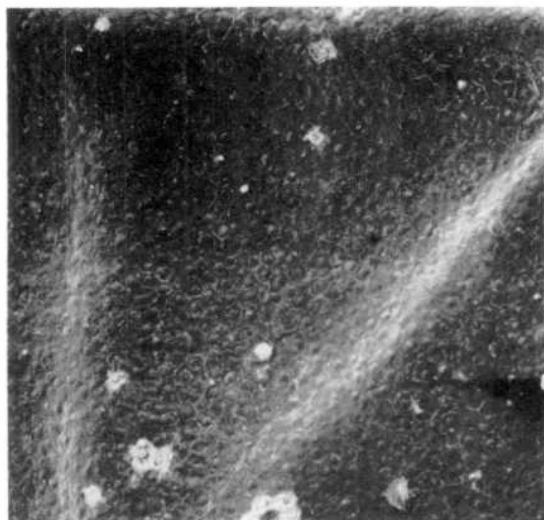


Fig. 3A

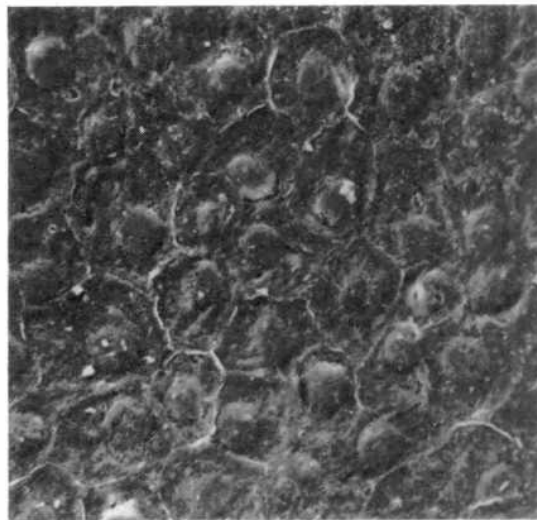


Fig. 3B

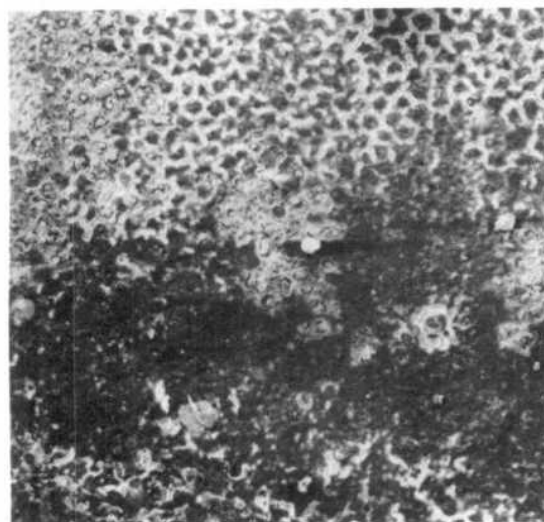


Fig. 3C

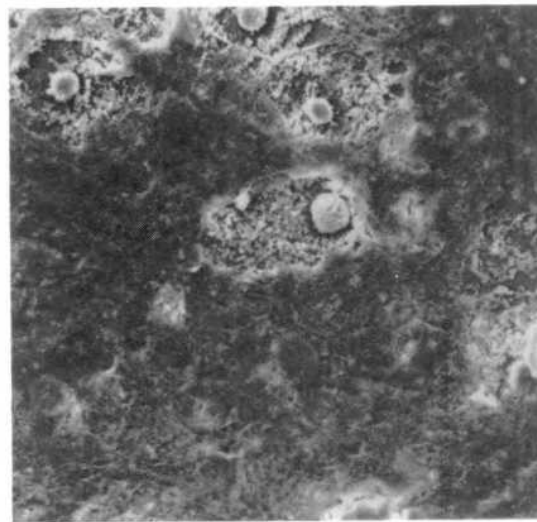


Fig. 3D

Fig. 3 Human corneal endothelial cells after 16 days of storage in K-Sol. The corneas had been stored in K-Sol with antioxidants for two days by the eye banks from which they were obtained. On arrival in our laboratory the corneas were washed and transferred one each into K-Sol with antioxidants (A and B) and K-Sol without antioxidants (C and D). The corneas were removed from storage 14 days later and processed for scanning electron microscopy. (A and C, $\times 160$; B and D, $\times 800$).

were not in the detectable range, the endogenous levels of glutathione in the endothelium of corneas stored in M-K medium did not show significant change over 14 days of storage.¹¹ These authors¹⁰ also reported that the amount of oxidised glutathione, which is toxic to endothelium, decreased from 12.6% in fresh corneas to 4.0% in corneas stored in M-K

medium for 14 days. Since K-Sol contains components essentially similar to those in M-K medium, except for the 5% dextran in M-K medium which is replaced with 2.5% chondroitin sulphate in K-Sol, it is reasonable to assume that most of the glutathione may remain in reduced form.

Although it is clear that antioxidants are necessary

for the preservation of endothelial cell morphology in corneas stored in K-Sol medium, the relative importance and optimum levels of various antioxidants are not known. Future studies are needed to define the role of particular antioxidants and the optimum levels of these substances to preserve corneal endothelial cells during long-term storage in preserving media such as K-Sol.

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Cutaneous anthrax leading to corneal scarring from cicatricial ectropion

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SUMMARY Eleven patients with cutaneous anthrax of the eyelids are presented. The complications were cicatricial ectropion (eight patients), resulting in corneal scarring (three patients). The ectropion was corrected by full thickness postauricular skin grafts, with good results. The predilection of this infection for the eyelids of young children and a seasonal variation suggest that a vector may be involved in transmission.

Anthrax is an infectious disease of the skin and respiratory or gastrointestinal tracts, caused by the Gram-positive sporing *Bacillus anthracis*. The spores of *B. anthracis* are notoriously hardy and long-lived. They can resist temperatures of over 100°C for prolonged periods, and are resistant to drying. They can remain dormant but potentially infective for over 20 years. Tissue damage in the host is caused by a complex exotoxin which damages the capillary endothelium and causes inhibition of phagocytosis.¹

Anthrax is a zoonosis, the main reservoir of infection being domestic herbivores such as cattle, goats, and sheep. Man can become infected through direct contact with contaminated skins; inhalation of spores from contaminated animal products, such as wool fibres or bone meal; or from eating infected meat. In addition it has been suggested that insects may act as vectors of infection from an infected animal to man.

The first sign of cutaneous anthrax is severe and massive oedema round the site of infection. The oedema can spread from a single lesion to involve the whole trunk. Oedema of the neck may be of such severity as to obstruct the airway, necessitating tracheostomy. The oedema is characteristically non-pitting, and has been described as 'gelatinous'. At this early stage translucent epidermal bullae and vesicles often surround the lesion – the so-called 'pearly wreath'. As the oedema subsides, a characteristic pustule and area of tissue necrosis develops at the site of inoculation (Fig. 1). This forms a black slough, known as the eschar or charbon (Fig. 2).

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After two to four weeks the eschar sloughs away, leaving an area of exposed granulation tissue, which heals with scarring. If the lesion is on the eyelids, scarring and contracture occur and may lead to cicatricial ectropion.²

Before the advent of antibiotics, and today in rural areas of the developing world where antibiotics are often not available, cutaneous anthrax may lead to septicæmia, which has a mortality rate of 20-30%. Parenteral penicillin in high doses is still the recommended first line treatment.¹

This paper reports a series of 11 patients with periocular anthrax and its complications seen at Mvumi Hospital, Tanzania. Mvumi Hospital is an Anglican mission hospital 26 miles south-east of Dodoma in the centre of Tanzania. This is one of the driest, least fertile, and poorest regions of the country. The local people, the Wagogo, are mixed farmers, growing millet and keeping large herds of cattle and goats. They have a high incidence of eye disease, particularly trachoma, and the prevalence of blindness (binocular visual acuity less than 3/60) is 1.6%.³

Patients

Between January 1984 and June 1988 11 patients with periocular anthrax or its sequelae were admitted to the Mvumi Hospital Eye Unit (Table 1). Six presented with acute anthrax of the eyelids and five with late sequelae. In patients who presented late the diagnosis was based on the presence of characteristic scarring and a history of severe swelling and black eschar formation prior to the development of the ectropion.



Fig. 1 Severe eyelid oedema and early eschar formation in cutaneous anthrax.



Fig. 2 The oedema has now resolved, leaving the black eschar.

The main complications seen were cicatricial ectropion (eight patients) and corneal scar secondary to exposure from ectropion (three patients).

Six females and five males were affected. Seven patients were children. The age range was 4 months to 45 years at the time of infection. The upper lid was affected in six patients and the lower lid in five. There appeared to be a seasonal trend, with the onset of infection being more common during the rainy season.

The six patients with acute anthrax were treated with high doses of parenteral penicillin. None developed anthrax septicaemia. Three developed ectropion, and three healed with scarring but without ectropion: these three had anthrax of the lower lid.

Eight patients with cicatricial ectropion (six upper and two lower) had their contractures released and a full thickness postauricular skin graft performed. In seven patients this was uncomplicated and a satisfactory resolution of the ectropion was achieved. In

one patient the skin graft became necrotic because of infection with a polyresistant staphylococcus, though correction of the ectropion was still satisfactory.

Corneal scar secondary to exposure occurred in three patients. These were all children who presented two to four years after the acute infection and had severe cicatricial ectropion, shortening of the upper eyelid, and exposure of the cornea.

Discussion

The main complication of periocular anthrax is cicatricial ectropion. This occurred in eight of 11 patients. Two out of five patients with lower lid anthrax developed ectropion, compared with six out of six for upper lid anthrax, suggesting that anthrax is more likely to cause ectropion when it affects the upper lid.

Exposure and corneal scar were associated with ectropion of the upper lid in three patients. The

Table 1 Clinical features of 11 patients with cutaneous anthrax of the eyelid

Patient	Age	Sex	Lid	Presentation			Complications	
				Mode	Interval from first symptoms	Month of first symptoms	Ectropion	Corneal Scar
1	25	M	RL	Acute	10 days	May	No	No
2	4	F	LL	Acute	1 week	June	No	No
3	45	F	LL	Acute	1 week	Jan	No	No
4	4 months	F	RL	Acute	2 days	Nov	Yes	No
5	2	F	RU	Acute	1 week	Jan	Yes	No
6	26	F	RU	Acute	2 weeks	Jan	Yes	No
7	3	M	LU	Late	3 months	April	Yes	No
8	26	M	RL	Late	Unknown	Unknown	Yes	No
9	2½	F	RU	Late	2 yr	Unknown	Yes	Yes
10	5	M	RU	Late	Unknown	Unknown	Yes	Yes
11	12	M	LU	Late	4 yr	Unknown	Yes	Yes

RL=right lower, LL=left lower, RU=right upper, LU=left upper.

corneal scar was considered blinding in the patients with this complication, though two were too young to have their visual acuity measured. Since the six patients with upper lid ectropion all had a good result following skin grafting (that is a complete resolution of the ectropion and good lid closure), it seems probable that these corneal scars could have been prevented by earlier diagnosis, referral, and skin grafting. Three out of the seven children with periocular anthrax were blind in the affected eye.

Anthrax in this series appears to be more common during the rainy season than the dry, which is in accordance with a study from Zimbabwe,⁴ though a study in the Gambia found the highest incidence during the dry season.⁵ The seasonal variation parallels that of other vector borne diseases in the area, such as malaria and trachoma. It has been presumed that the most likely way of acquiring infection is direct contact with infected skins, though this would be unlikely to cause a seasonal variation.

During the period when six patients presented with acute periocular anthrax only two patients were admitted with anthrax of other parts of the body. This finding is difficult to explain if infection is acquired from direct contact with animal skins, which are in contact with the whole body when used as bedding. Moreover, if the main route of infection was contact with infected animals or animal products, it is surprising that over half of our patients were under 6 years old, as this group of the population has very little contact with livestock, which are cared for by older children and adults.

Although direct transmission from infected animal products, particularly skins, probably does occur, the predilection for the eyelids of children suggests other possible modes of transmission. Flies are commonly found on the face and round the eyes of small children, who consequently frequently rub their eyes. It is possible that the anthrax bacillus is transferred to the children's eyelids either by flies or by self-contamination from their own fingers after

handling contaminated animal skins used for bedding.

The survey of anthrax in Zimbabwe between January 1979 and March 1980 reported 6000 cases. The peak incidence was during the rainy season, and it was suggested that a vector may be responsible for transmission. They also found that anthrax was more likely to occur on exposed parts of the body. A number of their patients gave a history of being bitten or stung at the site of the lesion prior to the development of anthrax.⁴ However, none of the patients in our study volunteered such a history.

Conclusion

Cutaneous anthrax in this small series was responsible for cicatricial ectropion, resulting in corneal scar and blindness in the affected eye. The ectropion can be corrected with good results by full-thickness skin grafting. There is anecdotal evidence that the disease has a predilection for the eyelids and occurs more commonly in children and during the rainy season. This suggests either that transmission occurs from rubbing the eyelids with contaminated fingers or possibly that an insect vector may spread the bacillus from animals to the children's eyelids.

We acknowledge the support of Christoffel Blindenmission of West Germany, which made this work possible.

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Retinal vasculitis in human T-lymphotropic virus type I associated myelopathy

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SUMMARY Human T-lymphotropic virus type I (HTLV-I) has been recently found to be associated with slowly progressive myelopathy. We have seen 12 patients with HTLV-I associated myelopathy (HAM), three of whom showed retinal vasculitis. In addition two patients had ocular symptoms of vitreous opacity. Retinal vasculitis in these patients appears to be phlebitis and sheathing of retinal veins in the periphery of the fundus.

Human T-lymphotropic virus type I (HTLV-I) was isolated from T-cell lymphoma and adult T-cell leukaemia^{1,2} and is now considered to be the causative agent of adult T-cell leukaemia/lymphoma. Recently HTLV-I was found to be associated with chronic myelopathy of unknown aetiology, that is, tropical spastic paraparesis (TSP) in equatorial countries, Martinique, Jamaica,³ off the pacific coast of Colombia,⁴ and Seychelles Island.⁵ Moreover, in south-western Japan, which is in a temperate zone, HTLV-I was found in patients with slowly progressive myelopathy. Osame *et al* suggested that the Japanese myelopathy, HTLV-I associated myelopathy (HAM), is a distinct clinical entity because it has not been found in a tropical area.⁶⁻⁸ It is believed that HAM is essentially the same as HTLV-I associated TSP, because their clinical features resemble each other.^{7,8}

The prevalence of HTLV-I carriers in the healthy population is about 10% in south-western Japan, and HTLV-I has been found to be transmitted by breast feeding, sexual contact, and blood transfusion. The proportion of HAM cases in the carrier group is estimated to be 1 to 2000, and 556 patients with HAM have been registered so far throughout Japan.⁸ In our experience patients with HAM often complain of ocular symptoms. So far we have examined ophthalmologically 12 patients with HAM. Five were found to have ocular changes; retinal vasculitis was seen in three of them. To our knowledge retinal vasculitis in

patients with TSP or HAM has not been reported previously. The present report describes three such patients.

Case reports

CASE 1

A 58-year-old woman came to our clinic in 1981 with a six-year history of slowly progressive gait disturbance. She also had sensory and sphincter impairment. She had a history of an operation for pituitary tumour in 1979.

On the first visit to our clinic in 1981 her visual acuity was 20/20 in each eye. Funduscopic examination showed sheathing of the retinal veins and phlebitis in the periphery of the fundus with vitreous haze in both eyes. A slight visual field defect was observed on the temporal side of both eyes, probably due to residual defects from the previous resection of the pituitary tumour. The sheathing of the veins has gradually extended posteriorly towards the disc. In July 1987 the blood serum and cerebrospinal fluid (CSF) were found to be positive for antibodies to HTLV-I. Her husband was also seropositive for HTLV-I. In August 1987 she was started on corticosteroids orally, and the gait disturbance improved slightly. In November 1987 her visual acuity was 20/25 in each eye. There were posterior subcapsular cataract and vitreous haze bilaterally, sheathing of the veins over the entire periphery of the fundus, obliteration of arteries, and optic atrophy in both eyes. A fluorescein angiogram showed macular oedema, disturbance of the pigment epithelium, and

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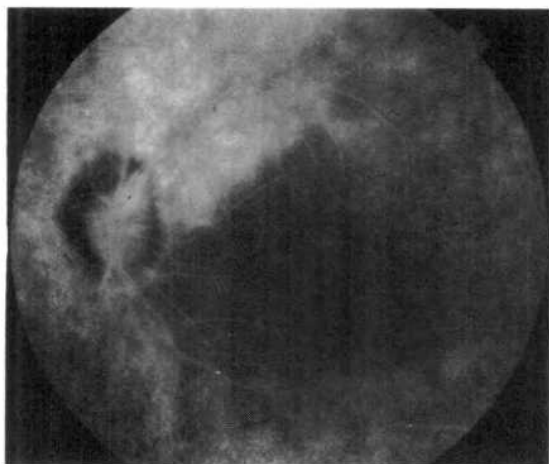


Fig. 1 Case 1, left eye. Fluorescein angiogram shows fluorescein leakage from the choroid and retina, disturbance of the pigment epithelium, and slight macular oedema.

fluorescein leakage from the retinal capillaries in the posterior fundus (Fig. 1). When the vitreous opacity increased, cells appeared in the anterior chamber.

CASE 2

A 49-year-old woman was admitted to the neurology department in October 1987 because of gait disturbance which had been slowly progressing for the previous five years. She also had sphincter impairment. Her serum and CSF were positive for antibodies to HTLV-I. Her husband and mother were also seropositive for HTLV-I. She was started on an oral corticosteroid preparation for myelopathy in

August 1986, and the gait disturbance has been improving.

She was referred to us in September 1987 for investigation of blurred vision in the right eye that had persisted for 10 months. Her visual acuity was 20/25 OD and 20/20 OS. A large number of cells were present in the anterior vitreous in the right eye, and minimal vitreous haze was noted in the left eye. There were also some cells in the anterior chamber of the right eye. Sheathing round the veins and whitish floaters close to the retina were noted in the periphery of the inferior fundus in the right eye. Fluorescein angiogram disclosed phlebitis and hyperfluorescent areas in the same lesions (Fig. 2). During the past year the sheathing round the vein has slowly progressed towards the posterior fundus from the periphery.

CASE 3

A 50-year-old woman developed pneumonia in March 1987 followed one month later by blurred vision in both eyes. She began to stumble easily and became unable to keep herself in a standing position in August. Gait disturbance had gradually progressed to the point where she was no longer able to walk and stand in October. Sphincter impairment also developed in November. The serum and CSF were positive for antibodies to HTLV-I. She had no history of blood transfusion, and her family history contributed nothing.

When she was first examined in November 1987 her visual acuity was 20/20 in each eye. Many cells were floating in the anterior vitreous of both eyes, though the anterior chamber and lens were clear. Snowball-like opacities were noted in the lower part

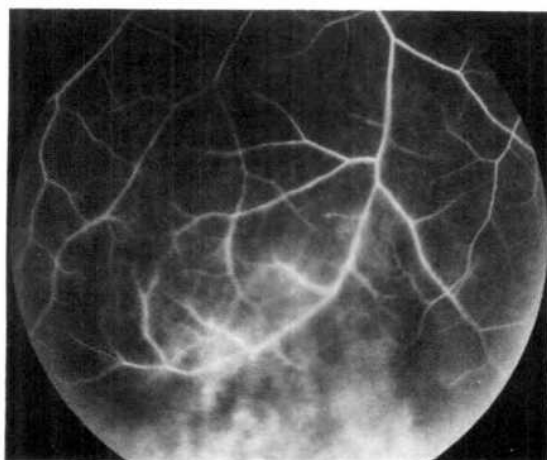


Fig. 2 Case 2, right eye. Fluorescein angiogram shows phlebitis and hyperfluorescent area in the same lesion.

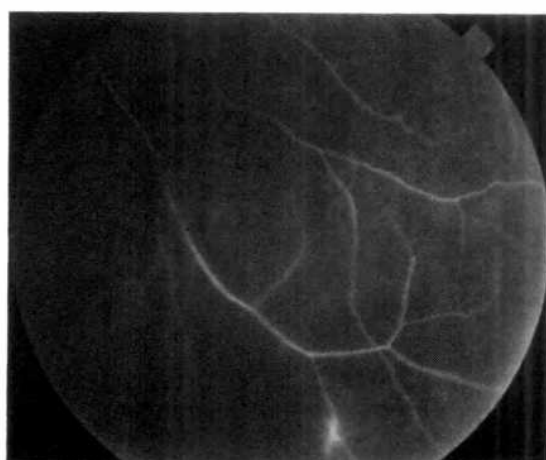


Fig. 3 Case 3, left eye. Fluorescein angiogram shows phlebitis in the periphery of the inferior fundus.

of the vitreous, and fluorescein angiogram showed phlebitis at 6 o'clock in the periphery of the fundus in the left eye (Fig. 3). There was sheathing of the vein in the periphery of the inferotemporal fundus in the right eye, but a fluorescein angiogram did not show any inflammatory changes. Interferon was given for the myelopathy, and the gait disturbance was slightly improved. It is of interest that retinal vasculitis of the left eye disappeared.

CLINICAL FEATURES OF THE THREE PATIENTS

The three patients had no lesions in the mucosa or skin (that is, ulceration of the buccal mucosa or external genitalia or erythema nodosum). They had no history of tuberculosis, and chest x-rays were normal. The laboratory data showed normal blood counts, blood chemistry, and urine analysis. The levels of angiotensin-converting enzyme in the sera were within the normal range, and serum tests for syphilis, rheumatoid arthritis, and lupus erythematosus were also negative. The serum titres of IgM and IgG antibodies against toxoplasma, herpes zoster, herpes simplex, and cytomegalovirus were low in cases 2 and 3, while IgG antibody against CMV was moderately raised in case 1. Serum antibody to human immunodeficiency virus was negative in all patients. Anti-HTLV-I antibody titres in both sera and CSF, tested by the particle agglutination method, were strongly positive.

Discussion

We examined 12 female patients with slowly progressive myelopathy in whom the disease had its onset in adult life. Anti-HTLV-I antibodies were demonstrated in the sera and CSF of all of them. Further investigation failed to show the cause of the myelopathy, leading to the diagnosis of HTLV-I associated myelopathy (HAM). Among the clinical findings in cases of HAM and HTLV-I associated TSP not only neurological signs but also alveolitis,⁹ Sjögren's syndrome, and keratoconjunctivitis³ have been reported. We found retinal vasculitis in three patients with HAM. Two additional patients also presented ocular symptoms with vitreous opacity, though the funduscopic examination, including fluorescein angiography, showed no retinal vasculitis. Although retinal vasculitis extended to the posterior fundus with macular oedema and optic atrophy in case 1, the periphery of the fundus should be considered to be first involved by the vasculitis. The retinal vasculitis of these patients is characterised by phlebitis and sheathing of the veins at the periphery of the fundus.

As a cause of retinal vasculitis the coexistence of sarcoidosis, Behçet's disease, syphilis, collagen disease, and tuberculosis were ruled out. In case 1,

IgG antibody against CMV was moderately raised. CMV retinitis is usually encountered in the newborn, in patients with an immunodeficient condition as a consequence of treatment for malignancy, or in patients with acquired immune deficiency syndrome (AIDS).¹⁰ However, immunodeficiency is not usually found in HAM patients, and our three patients had no clinical signs to suggest immunosuppression. CMV retinitis has characteristic appearances, including retinal haemorrhage, cotton-wool spots, and necrosis,¹⁰ which were not observed in case 1. The raised titre of IgG and the normal level of IgM antibodies against CMV may merely be a sign of past inapparent infection with this virus. Although non-infectious retinal vasculitis may be observed in AIDS,¹¹ tests for serum antibody to human immunodeficiency virus were negative in our three patients. The above data suggest that retinal vasculitis is a part of the findings associated with HAM.

The mechanisms for the neurovirulent nature of HTLV-I remain speculative. A slow viral infection may directly infiltrate the nervous system, or an immune reaction provoked by viral infection may attack the nervous system.⁷ Necropsy findings in one HAM patient showed vasculitis in the spinal cord, pons, cerebrum, and cerebellum.¹² It is of interest that vasculitis could be observed by funduscope in the retina, which is a part of nervous system.

Recent reports have suggested that a retrovirus similar to HTLV-I or III might play a part in the development of multiple sclerosis (MS).¹³ However, the neuropathological features of HAM¹² are different from those of MS, and the waxing and waning clinical course in MS is against the slowly progressive nature of HAM. Uveitis has been found in 27% of MS patients.¹⁴ They have sheathing of the veins and phlebitis in the periphery of the fundus, which are characteristic findings seen in HAM patients. However, optic neuritis, which is frequently found in MS, was not seen in any of our HAM patients. Optic atrophy, seen in case 1, was thought to be due to the progression of vasculitis to the posterior aspect of the retina rather than optic neuritis.

There have been few reports of ocular changes associated with HTLV-I. Ophthalmologists working in areas where the infection is endemic need to be aware of eye lesions in patients with HAM and possibly other HTLV-I related diseases.

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Association between keratoconus and atopy

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SUMMARY Sixty-seven patients with keratoconus were classified according to atopic status. Keratoconus patients with and without atopy did not differ significantly with regard to sex, age of onset, or rate of keratoplasty, but patients with very high IgE levels were more prone to graft rejection. Atopy was less common in patients with unilateral keratoconus, and keratoconus occurred more frequently on the side of the dominant hand. There was a significantly lower frequency of HLA B7 in the keratoconus group than in the controls. No abnormalities of essential fatty acid metabolism were found in keratoconus patients with or without atopy. There was no social class bias in the group. The study included a brother and sister with keratoconus and atopy, and a non-atopic patient whose identical twin did not have keratoconus.

Keratoconus is a disease of unknown aetiology, although several studies have demonstrated an association with atopy.¹⁻⁹ Excessive eye rubbing has been considered a reason for this association, on the assumption that atopic patients are prone to conjunctival itching and irritation,^{14,7} but some form of shared inheritance of the two conditions has also been proposed.⁷ Other suggested aetiological factors include genetic mutation due to increased parental age.¹⁰ Increased and decreased frequencies of certain HLA antigens have been found in patients with keratoconus.¹¹⁻¹⁵

In this study 67 patients with keratoconus were classified according to the presence or absence of atopic conditions, and the clinical progress of patients with and without atopic disease was compared. The patients were investigated for other possible associations with keratoconus, in particular HLA A, B, and DR antigens and increased parental age. Levels of essential fatty acids were estimated, as an abnormality of essential fatty acid metabolism has been found in some atopic patients, but keratoconus patients had not previously been studied. An association was also sought for unilateral keratoconus, atopic status, and hand dominance. The study included a sister and brother with keratoconus, and a patient whose identical twin did not have the disease.

Patients and methods

Sixty-seven patients with keratoconus attending the Bristol Eye Hospital participated in the study. The great majority were attending the contact lens department or corneal clinic or had undergone keratoplasty. All were seen by one examiner (RJH). Information was obtained about occupation, parental age, a family history of keratoconus, a family history of asthma, eczema, or hayfever (parents and siblings only), and a personal history of these conditions. The age of onset, contact lens wear, and keratoplasty were noted. Patients who had undergone keratoplasty were questioned about episodes of graft rejection, and further information was sought from the hospital notes. The patients were examined on a slit-lamp and with a keratometer to confirm the diagnosis of keratoconus. When the patient had undergone keratoplasty, the diagnosis was histopathologically confirmed.

Blood was taken for serum IgE, HLA typing, and essential fatty acid estimation.* Essential fatty acid levels were compared with those of samples from 35 normal subjects taken under similar conditions. Patients were also prick tested for 16 common allergens by means of the Bencard testing solutions.

In the absence of an agreed definition of atopy a

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*Essential fatty acids were determined by gas liquid chromatography analysis of the methyl esters at the Efamol Research Institute Laboratory in Nova Scotia, Canada.

simple classification was devised for the study. Atopic diseases present a clinical spectrum, and the patients were therefore divided into three groups – atopic, possibly atopic, and non-atopic – on the basis of a clinical history of atopic disease (asthma, eczema, or hayfever) and three items of supporting evidence of atopy: (a) raised serum IgE (>80 kU/l), (b) positive skin tests (at least two 2+ responses), or (c) a family history of atopy (parents or siblings only). Patients were considered atopic if they had two or more atopic conditions clinically, or one atopic condition and at least two items of supporting evidence. Possibly atopic patients had either one atopic condition and one item of supporting evidence, or no atopic condition but at least two items of supporting evidence. Non-atopic patients had no atopic conditions, normal IgE, and less than two 2+ responses on skin testing. There were no patients with a clinical history of an atopic condition without supporting evidence, but such patients would also have been classified as non-atopic. After the initial examination patients were sent a questionnaire about hand dominance, the presence or absence of eye rubbing, the hand used to rub the eyes, and the eye most rubbed.

Results

ATOPIC CLASSIFICATION

A history of asthma, eczema, or hayfever was obtained from 38 of the 67 patients (56.7%), with the majority of these patients suffering from more than one atopic condition. Asthma occurred in 19 (28.4%), eczema in 21 (31.3%), and hayfever in 25 (37.3%). Fifteen patients had only one atopic condition: seven had hayfever, six had eczema, and two had asthma. Only one patient had vernal catarrh.

The atopic status of 59 patients was determined according to the classification above (Table 1). The data were incomplete for the remaining eight patients. Half the patients classified as possibly atopic did not have an atopic disease clinically. When the serum IgE levels in the different groups were compared, all but one of the non-atopic patients had levels less than 31 kU/l (Fig. 1). Nine patients had very high IgE levels of >1000 kU/l.

There were 45 males and 22 females. There was a

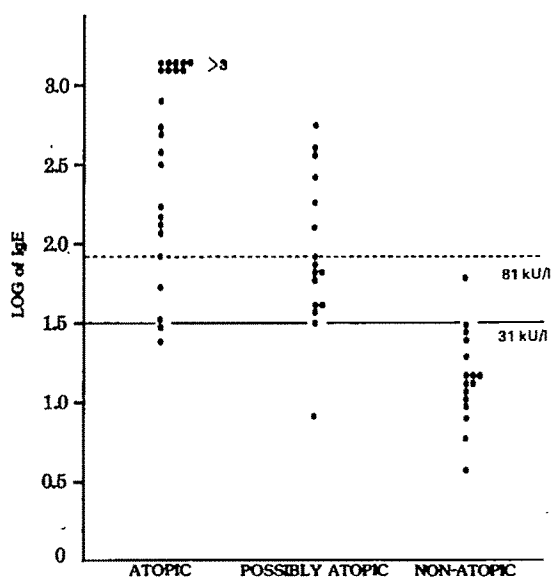


Fig. 1 Log serum IgE and atopic status.

greater proportion of males in the non-atopic group than the atopic and possibly atopic groups, but the differences were not significant. All the patients developed keratoconus in the second, third, or fourth decades, and age of onset did not vary significantly with atopic status. All the patients with clinical atopy, with one exception, developed keratoconus after the onset of atopic symptoms.

HLA ANTIGENS

HLA A and B antigens were determined in 57 patients, and 44 were typed for DR antigens. The HLA frequencies were compared with those of 586 random controls (Table 2). A highly significantly decreased frequency of B7 ($p<0.009$) and non-significant increased frequency of B5 ($p<0.16$) were found. There was no association with DR antigens. There were no correlations between HLA antigens and atopic status.

ESSENTIAL FATTY ACIDS

Plasma levels of all the essential fatty acids in both the

Table 1 Atopic status

	No. of patients	% of total
Not atopic	17	28.8
Possibly atopic	16	27.1
Atopic	26	44.1
Total	59	100

Table 2 HLA B5 and B7 frequencies (in %) in patients and controls

HLA	Patients n=57	Controls n=586	p
B5	14.0	9.0	0.16
B7	12.3	26.6	0.009

Table 3 Essential fatty acids (mean plasma levels)

		Atopic n=21	Possibly atopic n=16	Non-atopic n=16	Total n=59	Controls n=35
Linoleic	Mean	27.08	26.07	27.67	27.02	26.74
(18:2,n6)	SD	5.26	3.99	3.92	4.42	3.30
Dihomo- γ -linolenic	Mean	2.62	2.52	2.75	2.64	2.86
(20:3,n6)	SD	0.59	0.56	0.52	0.54	0.70
Arachidonic	Mean	10.96	10.49	10.81	10.76	11.10
(20:4,n6)	SD	1.67	1.23	1.96	1.62	1.55
Docosatetraenoic	Mean	0.316	0.287	0.275	0.300	0.334
(22:4,n6)	SD	0.18	0.19	0.13	0.17	0.20
Docosapentaenoic	Mean	0.222	0.263	0.218	0.240	0.314
(22:5,n6)	SD	0.17	0.22	0.12	0.17	0.26

linoleic (18:2,n6) and α -linolenic (18:3,n3) pathways were measured. The mean plasma levels of linoleic (18:2,n6), dihomom- γ -linolenic (20:3,n6), arachidonic (20:4,n6), docosatetraenoic (22:4,n6), and docosapentaenoic (22:5,n6) acids, the polyunsaturated fatty acids in the linoleic pathway, are shown in Table 3. The plasma levels of dihomom- γ -linolenic acid (20:3,n6) were lower in keratoconus patients than in controls, and levels in the atopic and possibly atopic subgroups were lower than the non-atopic group, but none of these differences were significant.

SOCIAL CLASS AND PARENTAL AGE

The social class of 65 patients was determined according to the Registrar General's classification and compared with data from the 1981 census for the South West Region (Table 4). Patients with keratoconus in this study did not show any social class bias. The year of birth ranged from 1908 to 1967, and the mean year of birth was 1953 (SD 11.75). The mean paternal age at time of patients birth was 31.4 years (range 19-57 years, SD 6.44) and the mean maternal age was 28.4 (range 18-42 years, SD 5.40).

KERATOPLASTY AND GRAFT REJECTION

The atopic status of patients who had undergone keratoplasty is presented in Table 5. Keratoplasty was more frequent in atopic patients, but this was not significant. Nine patients – five atopic, two possibly

atopic, and two not atopic – had at least one graft rejection episode, but there was no correlation between atopic status and graft rejection. Four of the five atopic patients with graft rejection had IgE levels >1000 U/ml, compared with only nine of all the 26 patients classified as atopic. This difference was significant (χ^2 test, $p<0.05$).

UNILATERAL AND BILATERAL KERATOCONUS, ATOPY AND HAND DOMINANCE

Keratoconus was bilateral in 46 patients. In 37 of these patients the disease developed simultaneously in both eyes, and in the remainder occurred in the second eye within five years. The duration of the disease in the bilateral group was from less than one to 35 years. Unilateral keratoconus was found in 21 patients, and the duration of the disease ranged from one to 57 years (Fig. 2). When the atopic status of these two groups was compared, atopy was less common in the unilateral group (Table 6). If patients with unilateral keratoconus for three years or less are excluded from the analysis, the differences in atopic status are significant (χ^2 test, $p<0.05$).

Unilateral keratoconus occurred in the right eye of 13 patients and in the left eye of only four, a difference that was significant (χ^2 test, $p<0.05$). This prompted a search for an explanation, so patients were sent a questionnaire about hand dominance and eye rubbing, and 48 replied. Two patients denied eye rubbing, and a third who was handicapped was unable to give reliable information. Of the remaining 45 patients 31 stated that they used both hands to rub

Table 4 Social class: keratoconus patients compared with the 1981 census results for the South-west Region (10% sample, persons by head of household)

Social Class	I	II	III	IV	V	Unclassified
Keratoconus patients, no.	4	16	29	8	2	6
%	6.2	24.6	41.5	12.3	3.0	12.3
South-west Region %	6.2	26.7	44.3	14.5	4.1	4.2

Table 5 Keratoplasty and atopic status

	Atopic	Possibly atopic	Non-atopic
Keratoplasty patients (numbers)	10	4	5
Keratoplasty patients (%)	52.6	21.1	26.3
Whole group (%)	44.1	27.1	28.8

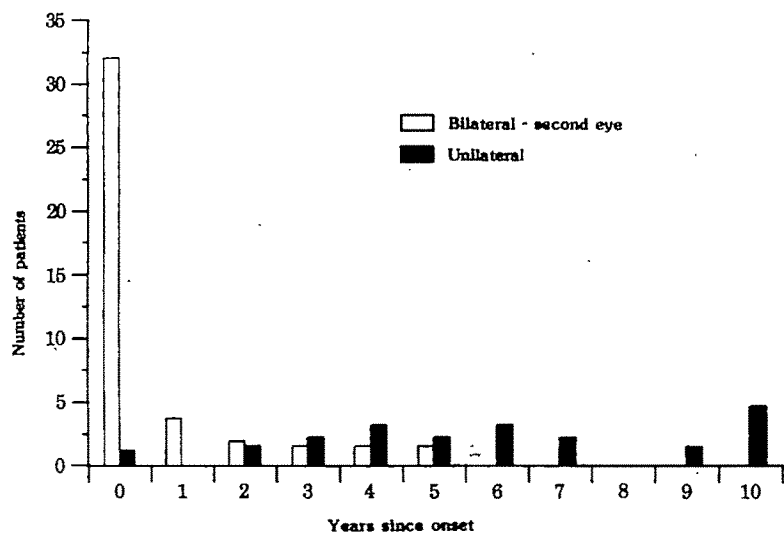


Fig. 2 Unilateral and bilateral keratoconus.

their eyes, 11 used their dominant hand, two used their non-dominant hand, and one ambidextrous patient used his right hand. In reply to the question about the eye mostly rubbed, 24 of 28 patients (85.7%) with bilateral disease felt they rubbed both eyes equally, compared with 10 of 16 (62.5%) with unilateral disease. This difference is significant (χ^2 test, $p < 0.05$).

Over three-quarters of patients with unilateral keratoconus (13 of 17) developed keratoconus on the same side as their dominant hand, a finding that is significant (χ^2 test, $p < 0.05$). Of the four patients who developed keratoconus on the opposite side, one stated that he used his non-dominant hand to rub the eye on the same side, two used, respectively, the dominant and both hands to rub both eyes, and only one stated that he developed keratoconus in the eye that he did not rub.

FAMILY HISTORY OF ATOPY AND KERATOCONUS

A family history of atopic disease in parents and siblings was reported in 86.4% of atopic patients, in 84.6% of possibly atopic patients, and in 23.1% of non-atopic patients. Two patients were sister and brother. The sister had suffered severe eczema from infancy and could remember being scolded for

rubbing her eyes as a child. She developed bilateral keratoconus at the age of 14 and underwent keratoplasty aged 30. Her younger brother developed eczema at the age of 20 and bilateral keratoconus the following year. He gave no history of excessive eye rubbing and was a successful contact lens wearer. Both brother and sister had high IgE levels (>1000 U/l and 800 U/l respectively). They shared one HLA haplotype, A31; B18; DR2.

One patient with a nine-year history of unilateral keratoconus had a twin who did not have keratoconus. Their physical appearance was strikingly similar, and their HLA type was identical. Both twins denied eye rubbing and neither was atopic, though both suffered contact dermatitis but from different irritants.

Discussion

The incidence of atopic disease in the general population is variously assessed as between 2 and 20%, and the proportion of the apparently non-atopic population that may suffer from atopic disease under suitable conditions is unknown.¹⁶ The presence or a previous history of atopic disease was noted in more than half the patients (56.7%) who participated in this study, and a further eight patients (11.9%) had evidence of atopy without clinical disease. Most previous studies have also found a high incidence of atopic disease,^{3,4,6,7,9} though some studies have failed to demonstrate an association.^{11,17}

Explanations for the high incidence of atopy in keratoconus patients have included an association or linkage between the genetic determinants of the two conditions, or eye rubbing stimulated by ocular

Table 6 Unilateral and bilateral keratoconus and atopy

Keratoconus	Atopic	Possibly atopic	Non-atopic	Total
Bilateral	22	8	11	41
Unilateral	4	8	6	18

itching or discomfort resulting from atopic disease,^{3,4} or a combination of both.⁷ Investigation for a possible genetic association presents particular difficulties, for while the atopic tendency is undoubtedly inherited the type and severity of atopic disease and the age of onset are variable even within a family group, and some individuals may have an atopic tendency demonstrated by a type 1 immune response on stimulation with low doses of common allergens (such as a positive skin test) in the absence of clinical disease.¹⁸ For this reason we used a set of criteria that distinguished the definitely atopic from the non-atopic, with a third intermediate group. The usefulness of this classification needs to be established by further studies, but it was encouraging to find that patients with normal levels of IgE but with evidence of atopy had levels mostly above 31 kU/l, while the opposite was true of patients without evidence of atopy: this did suggest that distinct groups had been delineated. A Swedish study of atopic and non-atopic populations found that a serum IgE level of 50.1 kU/l best discriminated the atopic and non-atopic groups.¹⁹

The hereditary nature of the atopic condition is well established, and a family history is obtained in about 70% of cases.¹⁶ It seems probable that at least three independent genetic systems operate in the acquisition of allergic illnesses.¹⁶ There is one (clearly critical) gene which predisposes certain individuals to develop one or more of the atopic diseases, but its chromosomal location and the mechanism of action of its translated products are unknown. A second genetic system controls total serum IgE levels and is not linked to either the genetic system mentioned above or the HLA system. Some workers have proposed that a single mendelian gene R/r plays a major role in the individual's IgE level, with the 'high IgE phenotype' corresponding to the rr genotype and the 'low IgE phenotype' corresponding to the RR and Rr genotypes.²⁰ Thirdly, there is a measure of HLA-linked genetic influence, and it has been postulated that several different Ir (immune response) genes associated with HLA type permit specific IgE synthesis in responders having high IgE phenotypes but that only one (or a very few) of such Ir genes allows response in people with low IgE phenotypes. This hypothesis would explain the strong association between particular HLA antigens and allergic responses to highly purified antigens in patients with low levels of IgE, but not in patients with high IgE levels.²⁰ Although an increased incidence of certain HLA types has been noted in some patients with an immune response to a particular antigen, no HLA associations have been demonstrated in atopic patients as a whole. It seems unlikely, therefore, that HLA associations found in keratoconus patients are

connected with HLA associations in atopic patients, unless atopic keratoconus patients showed a greater frequency of response to certain antigens than atopic patients without keratoconus. Although levels of HLA B7 were significantly decreased in our study, no independent associations between atopic status or IgE levels could be demonstrated. A statistically significant increase in the frequency of HLA B5,¹² HLA A9, A10, and A12,¹³ and HLA Bw21¹⁴ has been found in keratoconus patients, but other studies have found normal HLA frequencies.^{11,15}

Although research into atopy has naturally concentrated on the immunological aspects of the condition, there is some evidence that a disorder of fatty acid metabolism may be an aetiological factor. Essential fatty acids are the precursors of prostaglandins and leukotrienes, and are also important structural components of cell membranes. Reduced levels of an essential fatty acid derivative, dihomog- γ -linolenic acid, have been found in patients with atopic eczema and a deficiency of the δ -6 desaturase enzyme has been postulated.²¹ Patients treated with long-chain fatty acids to bypass this enzyme block have shown clinical improvement.²² If reduced levels of dihomog- γ -linolenic acid could be demonstrated in keratoconus patients, a genetic association between keratoconus and atopy could be proposed. Although we found reduced levels of dihomog- γ -linolenic acid in keratoconus patients which were lower in the atopic and possibly atopic groups than in the non-atopic group, these differences were not significant.

Karsenas and Ruben,⁴ Woodward,¹⁰ and Ihalainen²³ noted a bias towards the higher social classes in keratoconus patients, but this was not found in our study. Woodward¹⁰ also found a significantly higher maternal age in keratoconus patients than in the general population and argued that the social class bias was secondary to increased parental age, suggesting that a genetic abnormality related to parental age might contribute to the aetiology of the disease. Ihalainen found no maternal age bias,²³ and maternal age in our study was significantly lower than in the Woodward study. Details of this work have been published elsewhere.²⁴

Differences in the clinical course of keratoconus in atopic and non-atopic patients were compared in the hope that this might shed light on the nature of the association between keratoconus and atopy. Contrary to our clinical impression atopic patients did not have a significantly earlier onset of disease or higher rate of keratoplasty than non-atopic patients, nor were they more prone to graft rejection, though high levels of serum IgE may be a specific risk factor for rejection. The only significant clinical difference we found was a negative association between the more severe atopic manifestations and longstanding unilateral disease.

The proportion of unilateral cases in this study, at 31.3%, is comparable with other studies, where the proportion has varied from 5.8 to 41%.^{8,9,11,25}

Evidence for excessive eye rubbing as a causative factor in keratoconus has been found in a number of studies.^{1,3,4,7} There are obvious difficulties in quantifying the degree of eye rubbing either by observation or questioning patients, so we sought more indirect but objective evidence for it. Patients were questioned about age of onset of atopic symptoms and keratoconus, and in only one patient did keratoconus predate the onset of atopic symptoms. All but two atopic patients (who had asthma only) suffered with hayfever or eczema, the conditions most likely to cause ocular itching. To our knowledge no previous studies have reported a preponderance of right eyes in cases of unilateral disease. This preponderance, combined with the information that most patients use their dominant hand to rub their eyes, does support the view that eye rubbing influences the course of the disease. Patients with unilateral disease for more than three years were more likely to be non-atopic or possibly atopic, perhaps suggesting that eye rubbing in these patients was habit driven, whereas atopic patients were more likely to rub their eyes in response to bilateral ocular itching.

Keratoconus in identical twins has been reported previously,²⁶ as has keratoconus in one identical twin.²⁷ The occurrence of keratoconus in only one twin suggests that environmental factors are important, though the environmental factor most commonly suggested, excessive eye rubbing, was denied by both twins in our study. The frequency of inheritance of keratoconus has been found to vary between 6 and 19%.^{8,9,23,25,28} The sister and brother in our study both had high levels of IgE, but the range of IgE levels in this study does not support a genetic linkage between high IgE production and keratoconus. The onset of keratoconus was earlier in the sister who gave a history of excessive eye rubbing than the brother who denied excessive eye rubbing, suggesting that keratoconus is inherited with eye rubbing as an exacerbating but not a primary causative factor. Sister and brother had a common haplotype. Ihalainen reported on 15 families with more than one affected child and excess of haplotype sharing between the affected parent and children.²⁵

Conclusion

The relative contributions of genetic and environmental factors to the aetiology of keratoconus are poorly understood. An association with atopic disease was confirmed in this study, but the nature of this association is uncertain. A significantly decreased frequency of HLA B7 was found, but this showed no

independent association with atopic disease. Conflicting evidence for and against a genetic aetiology was provided by a patient with an identical twin who did not have the disease, and a brother and sister who were both atopic. There was some evidence that eye rubbing may contribute to the aetiology of keratoconus, as unilateral keratoconus occurred more frequently on the side of the dominant hand.

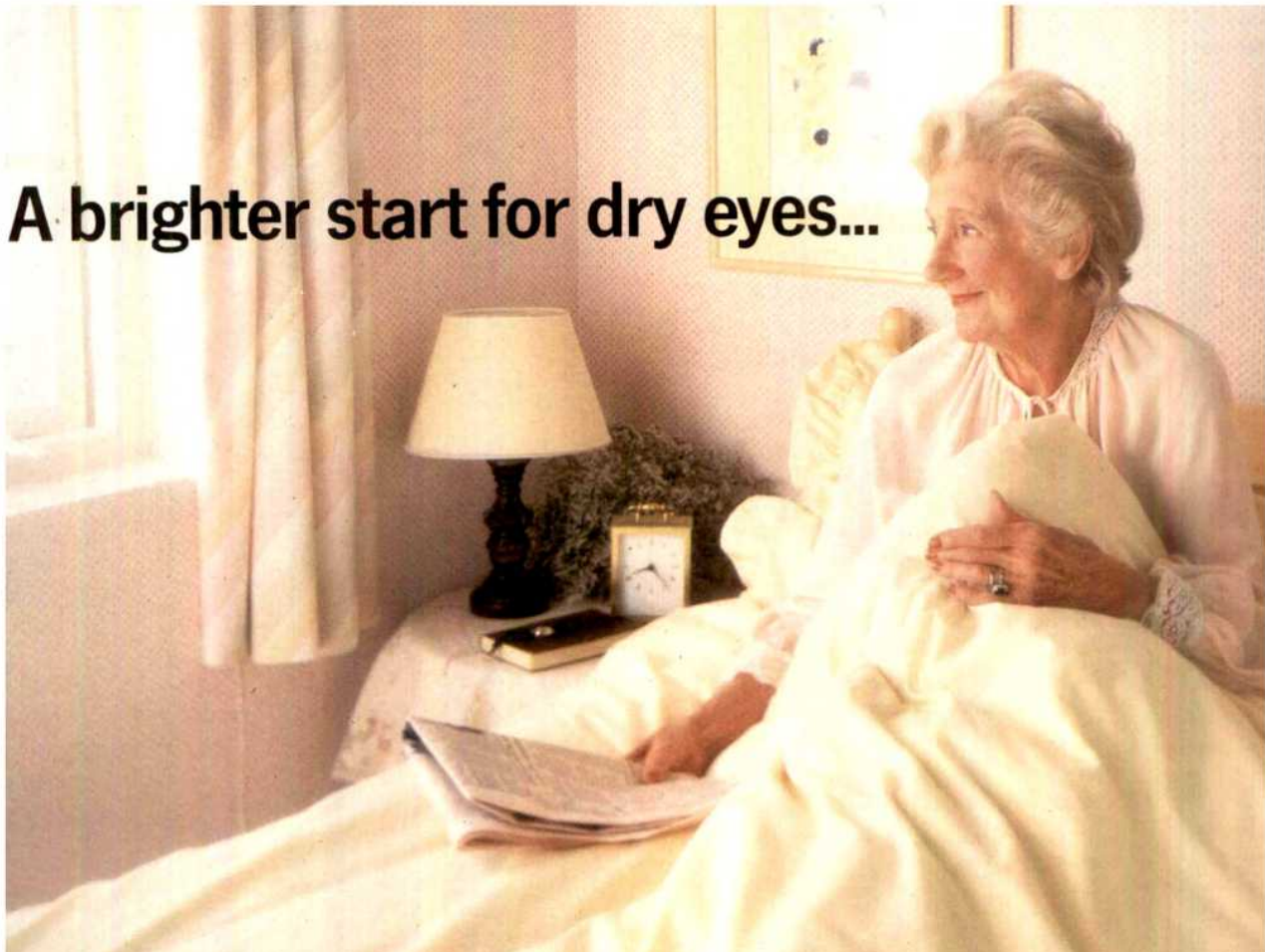
We thank Sister Bird and the nurses in the outpatient department and Mr Giltrow-Tyler from the contact lens department at the Bristol Eye Hospital. We also thank Ms Nicky Britten from the Department of General Practice, United Medical and Dental Schools of Guy's and St Thomas's Hospitals, London, for her assistance.

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A photograph of an elderly woman with short, wavy grey hair, wearing a light pink nightgown. She is sitting up in bed, covered with a white blanket, and holding a newspaper. The room is dimly lit, with a bedside lamp and a clock visible on a table next to her. A window with light-colored curtains is in the background.

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SRK II formula in the calculation of intraocular lens power

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SUMMARY We studied 400 eyes which underwent cataract extraction with posterior chamber intraocular lens (IOL) implantation to compare the predictive accuracy of various IOL power calculation formulae. The new Sanders-Retzlaff-Kraff (SRK) II formula was more accurate than the original SRK and Binkhorst II formulae. Modification of the A constants used in the SRK II formula to make it 'surgeon specific' improved its performance further; 80% of the eyes had less than 1 dioptre error and only one eye (0.3%) had an error of more than 3 dioptres.

Intraocular lens (IOL) implantation is at present the commonest method of visual rehabilitation after cataract extraction. Successful IOL implantation depends partly on the ability to predict postoperative refraction with accuracy. Numerous IOL power calculation formulae are available. They are either mathematical, based on theoretical optics,^{1,4} empirical, based on statistical regression analysis of a large number of implant patients,⁵⁻¹⁰ or a combination of the theoretical-empirical approaches.¹¹ There is no general consensus as to which approach or which particular formula is the most accurate.¹⁰⁻¹⁷ However, the Sanders-Retzlaff-Kraff (SRK) formula^{8,9} has become the most widely used for implant power calculation throughout the world.¹⁰⁻²² Sanders *et al*¹⁰ have recently introduced a new SRK II formula which has been shown to reduce the prediction error of the original SRK formula in short (<22 mm) and long (>24.5 mm axial length) eyes.

We routinely use the SRK formula to calculate IOL implant power. This study was carried out, firstly, to compare the predictive accuracy of the new SRK II formula with that of the original SRK and Binkhorst II formulae (see Appendix), and secondly improve if possible the results of the SRK II formula by modifying the constants used.

Materials and methods

This study was performed on 400 consecutive eyes which underwent cataract extraction followed by IOL implantation. All the eyes included in this study

had a final corrected visual acuity of 6/12 or better and postoperative astigmatism of less than 2.5 dioptres in cylindrical power.

IOL power was calculated on measurements of axial length and corneal curvature. All axial lengths were measured by applanation (A scan ultrasonography) with the Radionics Medical Oculometer™ 4100 system with a 10 MHz transducer. Corneal curvature was taken as the average of measurements in two meridians with an Inami BL-1 Keratometer. The power of the IOL implant was calculated by the software program within the ultrasound equipment system.

All the operations were carried out by the same surgeon (MSD). Cataract extraction followed by a posterior chamber IOL (IOLAB 107W modified Sinskey style, 10° angulated reversed optic lens) in the capsular bag was performed by the 'Intercapsular' technique.²³

Sutures were selectively cut or loosened in patients at four to six weeks postoperatively if they had a cylindrical power of 2.5 dioptres (D) or more. However, if the desired results were not obtained by this procedure, all the sutures were removed at eight weeks postoperatively. Refractions used in this study were carried out between six and eight weeks postoperatively.

We adopted the approach of Sanders *et al*¹⁰ and grouped our data base in subsets of short eyes (axial length less than 22 mm) and long eyes (greater than or equal to 24.5 mm), with average eyes in between. We derived separate A constants within each subset and used these values in our modification of the SRK II formula.

The original SRK formula was used to calculate the predicted emmetropic IOL power values for each patient. The deviations of the actual implant power from that predicted were converted to the dioptric spherical equivalent in the spectacle plane by the following formula:

$$\text{Deviation} = (P_1 - P_E) \times 1/CR + R_S,$$

where P_1 is the dioptric power of the actual implant used, P_E is the predicted emmetropic IOL power, CR is the ratio between the implant and the spectacle plane, and R_S is the observed postoperative refraction. We used a CR value of 1.25 for $P_E > 14$ D and 1.00 for $P_E < 14$ D.^{10,24,25}

This process of computing the difference between the actual and predicted postoperative refractive status of each patient was then carried out for the other IOL power calculation formulae under evaluation—Binkhorst II, SRK II, and our modification of the SRK II formula. We assessed the clinical significance rather than the statistical significance²⁶ of the difference in predictive accuracy of the above formulae on the basis of the following parameters: mean absolute deviation from emmetropia (in dioptres), standard error of the mean deviation and the distribution of the deviations (number of patients with actual postoperative refraction within 1 or 2 dioptres respectively of the predicted postoperative refraction).

Results

Our database consisted of 400 eyes with IOL implants. They comprised 65 short eyes (axial length <22 mm), 283 eyes of average axial length (22–24.49 mm), and 52 long eyes (≥ 24.5 mm).

The A constants we derived after dividing the above groups into subgroups were as follows: Average eyes: 118.4; short eyes: <20 mm – 119.9, 20 to <21 mm – 119.5, 21 to <22 mm – 119; long eyes: 24.5 to <26 mm – 117.3, ≥ 26 mm – 117. Hence we 'personalised' the A constants used in the SRK II formula to make it 'surgeon specific' as shown in Table 1.

Table 1 The surgeon-specific SRK II formula

If	L < 20,	$A_1 = A + 1.5$
If	20 $\leq$ L < 21,	$A_1 = A + 1.0$
If	21 $\leq$ L < 22,	$A_1 = A + 0.5$
If	22 $\leq$ L < 24.5	$A_1 = A$
If	24.5 $\leq$ L < 26	$A_1 = A - 1.0$
If	L > 26	$A_1 = A - 1.5$

L is the axial length of the eye (in mm).

A is the average A constant derived by the surgeon ('personalised' A constant).

A_1 is the recommended A constant for use in calculating IOL power.

Table 2 Comparison of the predictive accuracy of various IOL power calculation formulae.

Formula	Absolute error	Distribution of postoperative refractive error in dioptres: number of patients (percentage)		
		<1 D	<2 D	≥ 3 D
Binkhorst II	0.85 D (0.03)	292 (73)	383 (96)	4 (1.0)
SRK	0.84 D (0.03)	293 (73)	380 (95)	4 (1.0)
SRK II	0.82 D (0.03)	312 (78)	384 (96)	3 (0.8)
'Personalised' SRK II	0.79 D (0.03)	321 (80)	387 (97)	1 (0.3)

Table 2 shows the overall comparison in the predictive accuracy of different IOL power calculation formulae. All of them performed equally well in the number of cases within an error of 2 dioptres. When the percentage of eyes within 1 D error was considered, SRK II was better than the original SRK and Binkhorst II formulae, with 78% accuracy. The personalised or surgeon-specific SRK II formula improved this further; 80% of the eyes had less than 1 D error and only one case (0.3%) had an error of more than 3 D.

In the 'long eye' group (Table 3), the SRK formula performed poorly compared with the SRK II and

Table 3 Comparison of the performance of various IOL power calculation formulae in eyes grouped according to the axial length

<i>Formula</i>	<i>Absolute error: mean (standard error)</i>	<i>Distribution of postoperative refractive error in dioptres: number of patients (percentage)</i>		
		<i><1 D</i>	<i><2 D</i>	<i>≥3 D</i>
<i>Short eyes (<22 mm)</i>				
Binkhorst II	1.13 D (0.11)	42 (65)	59 (91)	2 (3.1)
SRK	1.08 D (0.10)	41 (63)	60 (92)	2 (3.1)
SRK II	0.97 D (0.09)	51 (79)	62 (95)	1 (1.5)
'Personalised' SRK II	0.87 D (0.08)	57 (88)	64 (98)	-
<i>Average eyes (22 to <24.5 mm)</i>				
Binkhorst II	0.80 D (0.3)	209 (74)	274 (97)	1 (0.4)
SRK	0.78 D (0.3)	218 (77)	272 (96)	1 (0.4)
SRK II	0.78 D (0.3)	218 (77)	272 (96)	1 (0.4)
'Personalised' SRK II	0.78 D (0.3)	218 (77)	272 (96)	1 (0.4)
<i>Long eyes (≥24.5 mm)</i>				
Binkhorst II	0.79 D (0.07)	41 (79)	50 (96)	1 (1.9)
SRK	0.89 D (0.8)	34 (65)	48 (92)	1 (1.9)
SRK II	0.82 D (0.07)	43 (83)	50 (96)	1 (1.9)
'Personalised' SRK II	0.75 D (0.06)	46 (89)	51 (98)	-

Binkhorst II formulae, especially in the percentage of eyes within 1 D error. The personalised SRK II formula produced the best results, with no case having an error of more than 3 D.

In the 'short' eye group (Table 3) both the SRK and Binkhorst II formulae predicted relatively inaccurately compared with the SRK II formula, with 35% or more of the cases having more than 1 D error. The personalised SRK II formula was again better than the SRK II formula: 88% of the cases achieved less than 1 D error, and no case had an error of more than 3 D.

Discussion

Calculation of the intraocular lens implant power is still a relatively controversial subject. Despite the availability of numerous formulae¹⁻¹¹ none has been proved superior in all clinical situations.^{10-17,24,25} This is mainly due to the presence of various surgeon-specific variables like the type of keratometer or ultrasound equipment used, style of IOL, and surgical technique adopted.^{16,17,21,27} Some authors have recommended that the ideal solution to this problem is for the individual surgeon to develop his own formula.^{28,29} However, not all ophthalmologists have the time or the resources to do this and hence have to depend on one of the readily available IOL power calculation formulae.

We chose to concentrate on the SRK formula for the following reasons: (1) It is the most widely used formula throughout the world and includes many users in the United Kingdom.¹⁷⁻²² (2) Improving this formula will mean more accuracy at no extra expense to the surgeon; some of the available formulae are expensive and would make the existing equipment obsolete. (3) It is a simple and elegant formula, and the constants used can be easily modified to make it surgeon-specific. Such modification has been shown to improve the predictive accuracy of the original SRK formula.^{17,20,21,27}

The SRK II formula can be calculated with the same equipment and program as that for the original SRK formula. We found it easy to use, since it merely needed appropriate adjustment to the A constant depending on the axial length of the eye under consideration; all other inputs were the same. This adjustment was necessary in 29% of the eyes which were not of average length.

It is evident from Table 2 that over all the SRK II formula was only marginally better than the SRK and Binkhorst II formulae. This is because the majority of the eyes are of average axial length, where the various IOL calculation formulae predict equally accurately. It is the short eyes² or long eyes⁸ which usually cause problems in the predictability after

calculation of IOL power. In both these groups the SRK II formula was clearly superior to the SRK and Binkhorst II formulae (Table 3).

We had no difficulty in 'personalising' the A constants used in the SRK II formula. This improved its predictive accuracy further (Tables 2 and 3). We had to modify the SRK II formula probably because of the difference in the distribution of ocular axial lengths between our data and those of Sanders *et al.*¹⁰ In our database, more eyes were less than 22 mm (16% versus 8%) and fewer eyes equal to or greater than 24.5 mm (13% versus 14%), with our average A constant weighted towards the short eyes as compared with that of Sanders *et al.*¹⁰ Moreover, the role of the rather ill defined surgeon-specific variables in affecting the performance of IOL power calculation formulae for the individual surgeon is well known.^{11,16,17,21,23}

Though there is no consensus on this subject, we used CR values of 1.00 for emmetropic IOL powers less than 14 D and 1.25 for emmetropic powers equal to or more than 14 D, as has been recommended.^{10,24,25} This means that a change of one dioptre in IOL power will produce a change in refraction at the spectacle plane of 1.0 D if the emmetropic IOL power is less than 14 D or 0.80 D if the emmetropic power is equal to or more than 14 D. This helps the surgeon to calculate mentally and choose an IOL of appropriate power when aiming for a desired amount of ametropia.

Induced corneal astigmatism following cataract surgery is well known. Selective suture cutting or loosening relieved astigmatism induced by tight suturing. No wound leaks or dehiscences occurred in any of our patients. Some patients, however, developed troublesome astigmatism in a different axis. All the sutures were removed in these patients because of our clinical impression that this procedure is better than further selective removal or loosening of the sutures. At present we are reassessing our management of postoperative astigmatism in the light of two recent reports. Firstly, Richards *et al.*³⁰ found that cutting sutures in the early postoperative period is effective for control of astigmatism, but this effect decays with time. In fact, there was no difference at three years between the cases in which sutures had been cut and those in which they had not been cut. Secondly, there is a rapid resolution of astigmatism in the first four months after surgery.³¹

The SRK II formula provides a high degree of predictive accuracy at no extra cost in terms of time or money to the users of the original SRK formula. The constants used can be easily modified by the surgeon to take into account surgeon-specific variables and thus improve its ability to predict IOL power.

Appendix

SRK formula¹⁴:

$$P = A - 2.5 L_1 - 0.9 K.$$

SRK II formula¹⁵:If $L_1 < 20$, $A_1 = A + 3$ If $20 \leq L_1 < 21$, $A_1 = A + 2$.If $21 \leq L_1 < 22$, $A_1 = A + 1$.If $22 \leq L_1 < 24.5$, $A_1 = A$.If $L_1 > 24.5$, $A_1 = A - 1$.Binkhorst II formula solved for IOL power¹⁶:

$$P = \frac{1000 N_2 \{ (1000 - VR_S) (N_2 r - ((N_1 - 1) L_2) - r R_S L_2) \}}{(L_2 - D) \{ (1000 - VR_S) (N_2 r - ((N_1 - 1) D) - r R_S D) \}}$$

where

P = Calculated IOL power.

A = A constant used with the original SRK formula.

 A_1 = Recommended A constant for use in calculating IOL power. L_1 = Axial length of the eye (in mm) preoperatively. L_2 = Axial length of the eye (in mm) postoperatively.

K = Corneal power in dioptres.

 r = Corneal power in millimetres radius. N_1 = Refractive index of aqueous and vitreous (1.336). N_2 = Refractive index of cornea (1.333).

V = Vertex distance (12 mm).

D = Anterior chamber depth (in mm) postoperatively.

 R_S = Postoperative spectacle refraction.

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Effect on the 24-hour diurnal curve of intraocular pressure of a fixed ratio combination of timolol 0.5% and pilocarpine 2% in patients with COAG not controlled on timolol 0.5%

G M MACLURE, R VOGEL, A STURM, AND B BINKOWITZ

From North Riding Infirmary, Middlesbrough, Cleveland

SUMMARY Eight patients with chronic open-angle glaucoma who had an intraocular pressure >24 mm Hg at some time during the day while taking timolol 0.5% twice daily were given the fixed ratio combination of timolol 0.5% with pilocarpine 2% (TP₂) twice daily. By comparing full 24-hour diurnal curves on timolol with those on TP₂ it was possible to show that all patients except one (at a single timepoint) had an IOP <22 mm Hg when changed to TP₂. The mean IOPs, the area under the diurnal pressure curve, and the diurnal variation were all significantly lower on TP₂ twice daily than on timolol 0.5% twice daily.

It has been reported¹⁻³ that up to 30% of patients with chronic open-angle glaucoma (COAG) will not experience fully adequate reduction of intraocular pressure (IOP) on timolol 0.5% twice daily. The commonest and most rational additional agent used with timolol is pilocarpine. Pilocarpine is usually prescribed three or four times a day because its duration of action is only 6-8 hours. In a previous study⁴ it was shown that, whereas timolol 0.5% plus pilocarpine 2% or 4% twice daily both improved IOP control significantly in patients not controlled (≤ 22 mm Hg) on timolol 0.5% twice daily, increasing the frequency of the pilocarpine from twice to four times a day had no beneficial effect on the level of control or on its smoothness. Thus it was shown that it was possible to combine timolol with pilocarpine in a twice daily regimen. The present study was undertaken to evaluate the efficacy of a fixed ratio combination of timolol and pilocarpine twice daily in patients with COAG whose IOP was not controlled by timolol 0.5% twice daily. In particular we wished to compare the diurnal variation on the two regimens, since this would best confirm or negate the value of this fixed combination in glaucoma management.

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Materials and methods

The timolol and pilocarpine combination contained timolol 0.5% and pilocarpine 2% (TP₂) at pH 6.8 produced by mixing a ready mixed timolol and pilocarpine solution with a buffering solution to raise the pH of the mixture just prior to being issued to the patients. It is known that formulated in this way the TP₂ mixture is stable for four weeks.

Patients with primary open-angle glaucoma (POAG) were selected who had been on timolol 0.5% (T) alone twice daily for at least two weeks and had an IOP in both eyes greater than 24 mm Hg at one point during a 24-hour period. Males or females were to be over the age of 18 years, with no evidence of acute ocular infection or inflammation and no history of ocular surgery or trauma. Other exclusions were current or recent contact lens wear within one month, a history of embedded corneal foreign body within one month, active herpetic keratitis or active corneal ulcer within three months, any corneal abnormality preventing reliable applanation tonometry, diseases known to affect retinal function acutely or to produce acute visual field loss, and abnormalities of the peripheral retina which might lead to retinal detachment while on a miotic.

Since there is no way of masking an ophthalmolo-

gist to the miosis caused by pilocarpine, this was an open study requiring eight patients to complete the protocol. All patients consented to participate after the objectives and procedures of the study had been explained fully to them and a full ophthalmological examination carried out. On the day before the TP₂ was to be given (day -1) all patients had 24-hour diurnal IOP measurements while still continuing to receive T twice daily in both eyes. The IOP was measured on day -1 at 0600, 1000, 1400, 1800, 2400, and 0600 the next morning (the morning of study day 1). Only patients with an IOP greater than 24 mm Hg for at least one timepoint entered the treatment period. All intraocular pressures throughout the study were taken by the same ophthalmologist (GMM) using the same applanation tonometer. Patients were admitted to hospital for the diurnal curve recordings.

On day 1 patients had one drop of TP₂ instilled in both eyes at 0615 (after the 0600 IOP readings). They were given a bottle of TP₂ with instructions to administer one drop into each eye at 0615 and 1815 daily until they returned in two weeks. The timolol 0.5% was discontinued.

On day 14 the patients had an ophthalmological examination on arrival at 0600; the diurnal curve of IOP was measured at the same times as on day -1. TP₂ was instilled at 0615 and finally at 1815 on day 14.

Adverse experiences were sought throughout the study. The investigator was asked to evaluate their severity and their relationship to the test medication. Any patient reporting photopsias or an increase in floaters during the study was to be taken off TP₂, excluded from further participation in this study, fully examined, and assigned to appropriate clinical follow-up.

All analyses were performed using the patient's worst eye defined as the eye with the greater IOP on day 1 at 0600 (the last diurnal curve measurement before TP₂ was administered). If the IOP was the same in both eyes, the right eye was chosen. To evaluate efficacy the baseline (T) diurnal curve was compared with that on TP₂. Comparisons were made by comparing the area under the diurnal curves, by timepoint analysis of differences in IOP, by the smoothness of the diurnal curves (<5 mm Hg range being used as a reference point).

POWER AND SAMPLE SIZE

From a previous study⁴ it was calculated that, with a standard deviation for IOP change of 3.0 mm Hg, eight patients would be sufficient to detect a 3.5 mm Hg difference in IOP between T and TP₂ with 80% power ($\alpha=0.05$, two tailed). In fact in this study the actual pooled standard deviation of the change from baseline of 2.2 mm Hg gave 80% power to detect a

change of 2.5 mm Hg ($\alpha=0.05$, two tailed). Similarly it was calculated that if the range of patients' IOPs over a 24-hour period had a standard deviation of 2.2 mm Hg, eight patients would suffice to detect a 2.5 mm Hg difference from the hypothesised range of 5 mm Hg with 80% power ($\alpha=0.05$, two tailed). The actual deviation found in the study was only 0.8 mm Hg, which gave the study 80% power to detect a 0.9 mm Hg difference from the 5 mm Hg range.

Results

Eight patients gave informed consent, entered, and completed the study. There were six males and two females with a median age of 60.5 years, range 51 to 70 years. All patients had both eyes treated in the study. No patients withdrew or were removed from the study. There were no protocol violators and no missing data. The mean of the IOPs on presentation—that is, prior to timolol therapy—was 27.87 mm Hg (range 18–26 mm Hg) for the right eyes and 30.25 mm Hg (range 24–36 mm Hg) for the left eyes. Five patients had an arcuate scotoma in at least one eye. The remainder had enlargement of the blind spot or general depression of light threshold. All eyes had one or more of the above visual field defects as measured on the Octopus 2000, program 33.

Analyses were performed as described above. The analysis of IOPs at each timepoint for both treatments addresses the efficacy 12 hours after the previous dose both at night and in the morning. Examinations on day -1 (the last day on timolol 0.5% twice daily as single therapy) at 1800 and on day 1 at 0600 (12 hours after the last dose of timolol 0.5% and immediately prior to the first dose of TP₂) measured the 12-hour efficacy of T. the 12-hour efficacy of TP₂ was measured on day 14 at 1800 and day 15 at 0600.

The data for all patients are shown in Table 1. The mean IOPs at each timepoint are summarised in Table 2 and shown graphically in Fig. 1. The difference between the mean IOP on T and that on TP₂ is significant ($p\leq 0.01$) at all timepoints. This is reflected further by the means of the areas under the diurnal curves. The mean area under the curves for the worst eye was 575.4 (SD 22.1) mm Hg/h on T and 428.3 (SD 47.1) mm Hg/h on TP₂. The mean difference was significant ($p\leq 0.01$).

Smoothness of diurnal control was indicated by the diurnal variation. Only one patient (no. 6) did not have a smoother curve while on TP₂ than on T, having a range of 3 mm Hg for each (Table 1). The mean reduction in diurnal variation for the eight patients' worst eyes was significant ($p\leq 0.05$): the mean diurnal variation for T was 4.9 mm Hg and for TP₂ was 1.9 mm Hg.

Table 1 Worse eye data (IOP mm Hg)

No.	Treatment Group	0600	1000	1400	1800	2400	0600	Number of Controlled Timepoints (IOP <22 mm Hg)	AUC*	Range of IOP (mm Hg)
1	TP ₂	20	18	18	17	18	20	6	437	3
	T 0.5†	25	22	21	21	22	25	2	534	4
	Change	-5	-4	-3	-4	-4	-5			
2	TP ₂	22	21	20	21	21	21	5	502	2
	T 0.5	26	24	22	23	29	38	0	609	7
	Change	-4	-3	-2	-2	-8	-7			
3	TP ₂	20	18	18	18	20	19	6	451	2
	T 0.5	28	25	23	24	23	27	0	587	5
	Change	-8	-7	-5	-6	-3	-8			
4	TP ₂	20	18	19	19	20	20	6	463	2
	T 0.5	26	24	22	22	26	27	0	583	5
	Change	-6	-6	-3	-3	-6	-7			
5	TP ₂	15	16	15	16	16	16	6	378	1
	T 0.5	26	22	22	22	25	26	0	566	4
	Change	-11	-6	-7	-6	-9	-10			
6	TP ₂	17	15	14	16	17	17	6	383	3
	T 0.5	25	23	22	25	25	25	0	580	3
	Change	-8	-8	-8	-9	-8	-8			
7	TP ₂	18	18	18	19	19	18	6	443	1
	T 0.5	28	25	23	22	24	27	0	583	6
	Change	-10	-7	-5	-3	-5	-9			
8	TP ₂	16	15	16	15	15	16	6	369	1
	T 0.5	26	23	22	22	23	27	0	561	5
	Change	-10	-8	-6	-7	-8	-11			

*Area under curve. †T 0.5=timolol 0.5%.

No adverse experiences were reported, but five patients reported a total of 10 ocular symptoms when receiving TP₂. There were three instances of headache, three of 'night blindness' (difficulty in seeing in reduced light due to miosis), two of blurred vision,

and one each of photopsias and eye irritation. Except for one report of 'night blindness' all the ocular symptoms occurred on the first day of treatment with TP₂ and had disappeared by day 14. One case of 'night blindness' was not reported on day 1 but was

Table 2 IOP means (mm Hg): worse eye

Hour	Treatment Group	n	Mean	SD	Minimum	Median	Maximum
0600	TP ₂	8	18.5	2.4	15	19.0	22
	T 0.5	8	26.3	1.2	25	26.0	28
	Change	8	-7.8*	2.5	-11	-8.0	-4
1000	TP ₂	8	17.4	2.0	15	18.0	21
	T 0.5	8	23.5	1.2	22	23.5	25
	Change	8	-6.1*	1.8	-8	-6.5	-3
1400	TP ₂	8	17.3	2.1	14	18.0	20
	T 0.5	8	22.1	0.6	21	22.0	23
	Change	8	-4.9*	2.1	-8	-5.0	-2
1800	TP ₂	8	17.6	2.0	15	17.5	21
	T 0.5	8	22.6	1.3	21	22.0	25
	Change	8	-5.0*	2.4	-9	-5.0	-2
2400	TP ₂	8	18.3	2.1	15	18.5	21
	T 0.5	8	24.6	2.2	22	24.5	29
	Change	8	-6.4*	2.2	-9	-7.0	-3
0600	TP ₂	8	18.4	1.9	16	18.5	21
	T 0.5	8	26.5	1.1	25	27.0	28
	Change	8	-8.1*	1.9	-11	-8.0	-5

*Significant change from base line, $p \leq 0.01$. T 0.5=timolol 0.5%.

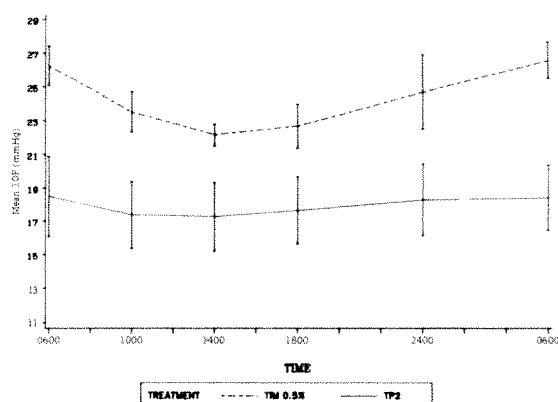


Fig. 1 Plot of baseline (timolol) and TP_2 diurnal curves. Means (with SD) for all patients: worse eye IOP (mm Hg).

reported on day 14. All of the ocular symptoms were mild in severity. There were no changes in visual acuity of either eye between day -1 (on T) and day 14 (on TP_2).

Discussion

The objective of this study was to show that a fixed combination of timolol and pilocarpine used twice daily would allow better and smoother control of IOP than timolol twice daily in those patients not responding adequately to timolol alone. The effects of the drugs were assessed by examining the extent of IOP lowering and the duration of action, as shown by the smoothness of the diurnal curves.

There is a potential for bias in this study, since the investigator would be clearly aware that the patients were on the test medication TP_2 . There is no way of disguising a bias to an ophthalmologist and thus no satisfactory way of controlling this study without introducing a third active agent, for example pilocarpine alone, which because of the time required for timolol washout would be to an undetermined extent additive and thus a rather confounded control agent. A comparison of activity of TP_2 with pilocarpine has been reported elsewhere.⁸

From comparison with pretreatment IOPs all patients except patient 4 in the right eye had shown some reduction in IOP when treated with timolol 0.5% twice daily.

Comparison of the diurnal curves showed significant lowering of IOP at all timepoints when patients received TP_2 in comparison with the same timepoints when patients received T. This held true when we examined the mean IOP of the worst eye and under the diurnal data curve. When all six timepoints for individual patients were examined, reductions in IOP at every timepoint were seen after patients had been

on TP_2 for 14 days; two patients had IOP reductions of as much as 11 mm Hg.

The value of this drug combination lies not in just the extent of the IOP lowering but also in the duration of the IOP lowering. It is important in the management of glaucoma that the IOP should be controlled (<22 mm Hg) throughout a 24-hour period. For many patients the pressure tends to be highest in the morning.⁶ Because TP_2 was given twice daily (every 12 hours), the extent to which the IOP was controlled could be determined by looking at the measurements taken at 0600, 1800, and 0600 the following day. These measurements were taken immediately before patients received their eye drops. Only one patient had the IOP controlled at two timepoints while receiving T; however, every patient except one at one timepoint had the IOP controlled at all timepoints after receiving TP_2 . For all patients there was significantly greater control of IOP after they received TP_2 than with T.

The smoothness of the diurnal curve was assessed by examining the range of IOPs along each curve. A smaller range of IOPs indicated a smoother or flatter diurnal curve. Patients receiving TP_2 had a smoother curve than when they received T. Of importance in assessing the efficacy of a drug for glaucoma therapy is the range of intraocular pressures obtained between doses. TP_2 was significantly better than T in this regard as shown by the smaller range of IOPs over the diurnal curve. The fluctuation or 'spiking' of IOP was smaller with TP_2 than with T.

The patients tolerated the combination well. No adverse symptoms or ocular signs were noted. Ten ocular symptoms were reported; all were mild and, except for one case of 'night blindness' had disappeared by day 14. 'Night blindness' is a descriptive term describing reduced visual function in poor illumination. In this study it is probable that, since all the patients were asymptomatic before receiving TP_2 the symptoms experienced were due to the introduction of pilocarpine into their regimen. The symptoms reported have all been reported on pilocarpine.⁷

The results of this study confirm findings in a previous study conducted by the same investigator¹ when 24 patients who had been on timolol received concomitant therapy of timolol 0.5% and pilocarpine 2% or if necessary pilocarpine 4%. Pilocarpine (2% or 4%) was administered twice or four times a day concomitantly with timolol 0.5% twice daily. In patients who received concomitant therapy the IOP was reduced significantly in comparison with timolol 0.5% alone. The patients receiving concomitant therapy also showed a smoother diurnal curve than when they received timolol 0.5%. In addition the study showed that there was no statistical difference between twice a day and four times a day dosing with

pilocarpine when used concomitantly with timolol.

In conducting the present study we hoped to show that a similar quality of IOP control could be obtained using a fixed combination of TP₂ to that shown in the previous study using concomitant timolol pilocarpine. To make real comparisons a further study using combination and concomitant administration in a randomly allocated, double-masked design would be required. The present study does, however, confirm the smooth nature of IOP control on TP₂ twice daily in patients whose IOP was inadequately controlled on timolol 0.5% twice daily.

Pilocarpine is usually administered every six hours; even if it is administered concomitantly only twice a day with timolol 0.5%, the patient is still required to administer four drops, that is, two of timolol and two of pilocarpine. With TP₂ the patient administers only one drop twice a day. Since compliance with a pilocarpine regimen has been shown to be poor, with patients administering a mean of only 76% of the prescribed doses and 30% of patients compressing their doses into 12 hours of the day⁸ it is likely that the use of a timolol pilocarpine combination twice daily will achieve better control and improved compliance in patients with glaucoma.

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Optic glioma of childhood: clinical, histopathological, and histochemical observations

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SUMMARY This report documents the long-term clinical and histopathological behaviour of eight intraorbital and 16 intracranial optic nerve gliomas and relates the therapeutic data to the prognosis for both visual acuity and survival. The mean age at onset of symptoms was 8.6 years and at the diagnosis 10.9 years. It is generally held that proptosis is mild in intraorbital glioma, but we encountered marked proptosis ranging from 7 to 12 mm in six of the eight intraorbital gliomas, which contained abundant Alcian-blue-positive mucoid material. Of the patients with intracranial optic nerve gliomas 37.5% survived for a mean of eight years after treatment with radiotherapy or surgery combined with radiotherapy. At follow-up ranging from five months to 11 years only one of the six patients with intracranial gliomas had full visual acuity. Our observations emphasise that, although optic nerve gliomas are benign hamartomas, the prognosis for visual acuity and survival is unfavourable in cases which are diagnosed and treated late. Histopathological and histochemical observations suggest that increase in the amount of mucoid material may contribute to rapid enlargement of intraorbital and intracranial optic gliomas.

Since the first description of optic glioma by Scarpa in 1816 much has been written on their natural course and treatment.¹ Most optic gliomas are low-grade pilocytic astrocytomas, and excision of the tumour results in a benign course. Malignant optic nerve gliomas are rare.² Death from intracranial optic glioma may be from mechanical pressure on vital structures, mainly owing to enlargement of the tumour.³ Anderson and Spencer³ emphasised the accumulation of mucinous material within the tumour as an important cause of its enlargement together with proliferation of neoplastic astrocytes and a reactive proliferation of arachnoidal tissue.

The present study reports the clinical findings and the effect of treatment on visual acuity and survival in children with histologically confirmed glioma of the optic nerve or chiasm. In addition, the effect of collateral meningeal hyperplasia and accumulation of mucoid material was studied histopathologically and histochemically as a possible mechanism for

enlargement of the tumour causing rapid exophthalmos or progressive deterioration of the patients' health.

Material and methods

The hospital records of 24 patients with histopathologically confirmed optic gliomas seen in the Departments of Ophthalmology and Neurosurgery at Hacettepe University from 1968 through 1982 were reviewed. Eight patients with orbital and 16 patients with intracranial optic gliomas were examined with regard to age, sex, and mode of onset of symptoms and signs. The surviving patients were followed up in an attempt to correlate the therapy with visual acuity and survival. The follow-up periods ranged from 5 months to 11 years, mean 8 years.

Sections of tumour blocks were prepared and histological verification of tumour cells was carried out in accordance with WHO criteria.⁴ All the sections were stained with haematoxylin-eosin, alcian blue, and mucicarmine for light microscopy.

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Results

Histopathological examination revealed in all cases that the tumour cells were mostly piloid astrocytes. In almost all these tumours microcystoid spaces contained different amounts of mucopolysaccharides staining positive with alcian blue (Fig. 1). In four of the six cases of prominent exophthalmos with intra-orbital glioma and in two of the cases of intracranial optic glioma (9 and 15 months old) histopathological evidence of mucosubstance to a greater degree than others was found by the alcian blue technique. Mucicarmine staining was negative in all tumours. The histopathological study showed collateral hyperplasia surrounding the optic nerve in two cases of intraorbital tumour with clinical evidence of severe exophthalmos (Fig. 2).

Frequency. During a 14-year period we found 24 cases of optic glioma of which eight were confined to the orbit. These tumours constituted 13.7% of the histopathologically diagnosed intraorbital tumours and were the most common orbital tumour during that period.

Localisation. In 16 cases the optic glioma was located intracranially. In 12 of these it was only chiasmal, and six patients had expansion of both optic nerves as well as involvement of the chiasm (Table 1). In five cases the third ventricle was involved and in one case the sinus cavernosus. In eight cases the tumour was located in the orbital part of the optic nerve alone.

Sex. Of the 24 patients 13 were male and 11 female.

Age. The range was 9 months to 53 years. The oldest patient had had relevant clinical symptoms 20 years before admission to the hospital. Table 2 gives the age onset of symptoms and the age at which the diagnosis was made in 24 patients with optic glioma.

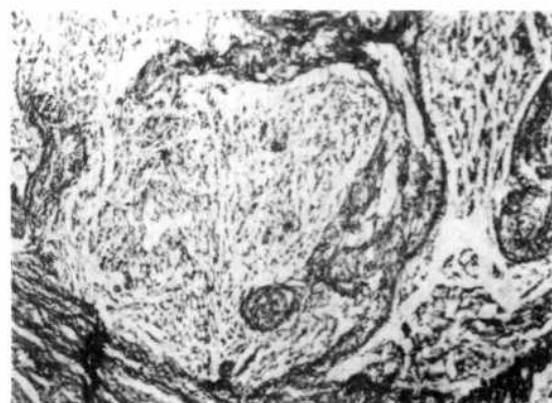


Fig. 1 Mucinous material in cystoid spaces in optic nerve glioma. (Haematoxylin-eosin).

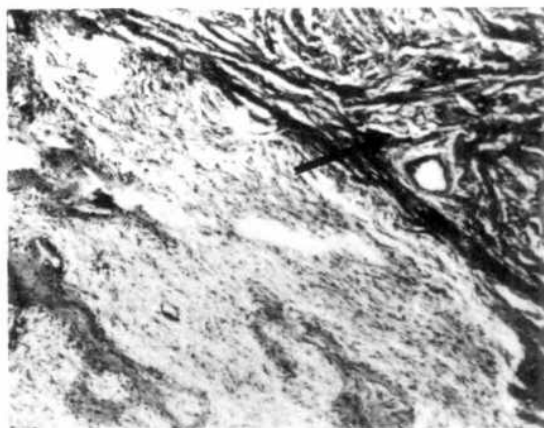


Fig. 2 Collateral hyperplasia surrounding the optic nerve glioma (arrow). (Haematoxylin-eosin).

The mean age at onset of symptoms was 8.6 years and at diagnosis 10.9 years. If the 53-year-old patient is excluded, the mean age at onset of symptoms would fall to 7.6 years.

The peak incidence of onset of the earliest symptoms was at ages 1–7 years, while the peak incidence at diagnosis was at 7–15 years.

Symptom and signs. Table 3 summarises the symptoms and signs of 24 patients grouped according to the initial symptoms and signs noted at first admission to hospital and during follow-up examinations. The first two most commonly encountered initial ocular symptoms in both groups were diminished visual acuity and exophthalmos. Diminished monocular visual acuity was present in eight patients with tumour confined to the orbit and ranged between absolute and 0.3 at the onset of the disease. The visual acuity of 16 patients with intracranial optic

Table 1 Localisation of optic nerve gliomas

Intraorbital glioma	8
Intracranial glioma	16
Chiasmal	12
Chiasmal+both optic nerves involved	6
Third ventricle involved	5
Sinus cavernosus involved	1

Table 2 Age of 24 patients with optic glioma at onset of symptoms and diagnosis

Age	Number of patients	
	Onset of symptoms	Diagnosis
Under 1	2 (8%)	2 (8%)
1–7	15 (62%)	9 (37%)
7–15	7 (29%)	13 (54%)

Table 3 Symptoms and signs in 24 patients with optic glioma

	Initial symptoms and signs on admission		Symptoms and signs at follow-up	
Ocular	Orbital	Intracranial	Orbital	Intracranial
Diminished visual acuity				
Monocular	8	6	8	—
Binocular	—	10	—	5
Exophthalmos	8	3	8	3
Strabismus	5	4	7	4
Nystagmus	—	3	—	6
Optic disc changes				
Papilloedema				
Unilateral	1	—	—	—
Bilateral	—	2	—	—
Optic atrophy				
Unilateral	6	6	8	3
Bilateral	—	10	—	4
Visual field defect	—	—	—	6
Others				
Increased intracranial pressure	—	8	—	12
Hydrocephalus	—	8	—	—
Multiple café au lait spots	6	—	6	—
Paresis	—	1	—	5
Acromegaly	—	—	—	1
Precocious puberty	—	1	—	1

glioma was usually extremely low owing to bilateral optic atrophy at first admission to the hospital.

All patients with intraorbital optic gliomas had exophthalmos. In six it was severe, ranging between 7 and 12 mm measured by Hertel exophthalmometer (Fig. 3).

The optic disc changes were usually of the optic atrophy type rather than papilloedema in whether intraorbital or intracranial tumours were the feature. Multiple café au lait spots were evident in six patients (25%). A 20-year-old woman with optic glioma also had an acoustic neurinoma, and a neurofibroma at the cerebellopontine angle as well as an intradural neurinoma extirpated at the level of L₁-L₄.



Fig. 3 A 6-year-old girl with an orbital glioma presenting with 12 mm exophthalmos in her left eye.

Table 4 Radiological findings in 24 patients with optic glioma

	Orbital optic glioma (n=8)	Intracranial optic glioma (n=16)
Enlargement of optic foramen	3 (37.5%)	12 (75%)
Enlargement of orbit	1 (12.5%)	—
Sella turcica	—	—
Enlarged pituitary fossa	—	3 (18.7%)
Deformed dorsum sella	—	6 (37.5%)
Calcification	—	4 (25%)
Separation of intracranial sutures	—	10 (62.5%)

RADIOLOGICAL FINDINGS

Table 4 indicates the radiological findings in the 24 cases. In 3 cases (37.5%) of intraorbital and in 12 (75%) of intracranial tumours an enlarged optic foramen with regular borders was noted (Fig. 4A,B). These three patients with enlarged optic foramen underwent both lateral and transfrontal orbitotomy and did not show any evidence of intracranial extension of the tumour.

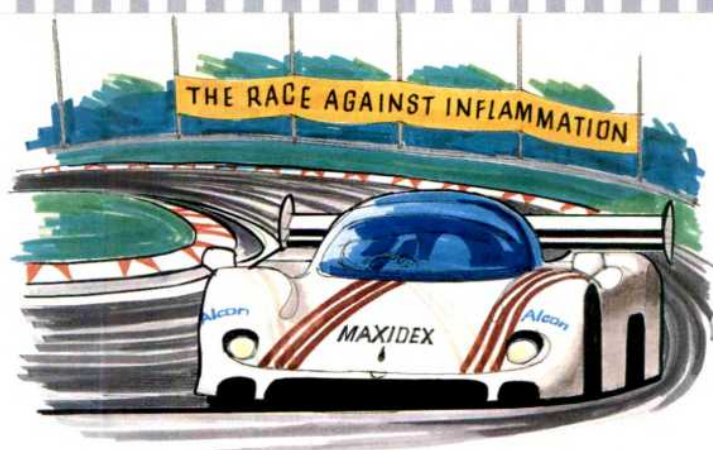
Two intracranial cases with chiasmal involvement showed bilateral enlargement of the optic foramen. A 20-year-old woman with complaints of six years' duration showed enlargement of orbital bones radiologically. Thirteen out of 16 cases of intracranial optic glioma had various radiological defects of the sella turcica (Table 4).

RELATION OF THERAPY TO VISION AND SURVIVAL

The types of treatment given in cases of orbital and intracranial optic glioma, and their relationship with tumour localisation and the patients' survival status, are summarised in Table 5. Five out of the total eight patients with intraorbital optic glioma had a modified Krönlein operation, and three other patients had a Krönlein operation and transfrontal orbitotomy.

The 16 patients with intracranial optic glioma underwent biopsy, subtotal or total tumour resection, and postoperative administration of 5500 rad radiation and carmustine (BCNU) therapy. Seven of the patients died within one month to seven years. These patients had extensive tumoural invasion of the chiasm and third ventricle. As an adjunct to other therapy ventricular shunts were performed in five out of eight patients with hydrocephalus diagnosed by pneumoencephalography. Three of these patients were still living at the time of study.

The survival status of three other patients was not known. Three out of six patients with intracranial optic glioma who underwent total or subtotal excision of tumour with postoperative radiation therapy were still living after 11 years. A mean duration of eight



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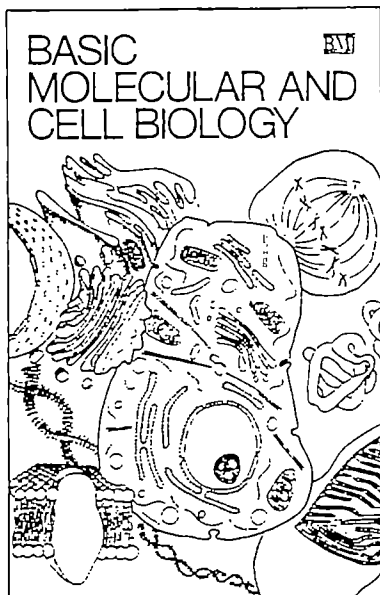
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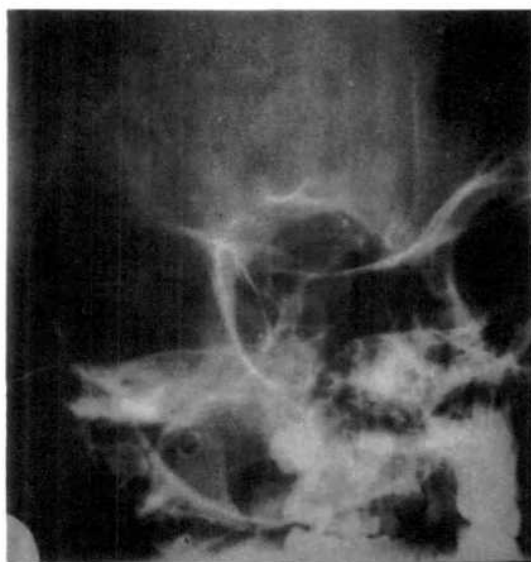


Fig. 4A

Fig 4 A: Orbital and intracranial optic nerve glioma in a 7-year-old girl. The normal left optic nerve canal. B: The right optic canal is enlarged to 8.5 mm diameter (arrow).



Fig. 4B

years' follow-up on our series of 16 patients showed 37.5% with intracranial optic glioma were alive.

The effect of therapy on visual acuity in 14 patients with optic glioma is given in Table 6. The visual acuity of patients with intracranial optic nerve glioma remained stable in low degrees. Only one patient had full vision after biopsy followed by radiation therapy.

Discussion

Optic glioma has been considered rare.^{1,2,4} In our series optic nerve glioma constituted 13.7% of all orbital tumours, thus being the commonest intra-orbital tumour. Most observers have reported that optic glioma is commoner in the chiasm than the optic nerves.^{5,10,11} The ratio of intracranial to intraorbital optic gliomas in our series was 2. The involvement of the chiasm in 12 cases of the intracranial optic gliomas and of the third ventricle in 5 supports the idea that they may be expansile, though they are accepted as being benign hamartomatous self-limiting tumours.

Lloyd⁷ and Yanoff and Fine¹² reported a preponderance of optic glioma in girls, contrary to our observations of an equal sex distribution which has been also reported by Henderson.⁵

There is general agreement on the congenital origin of this tumour owing to its appearing in infants and preschool children.^{10,13} Our study tends to

Table 5 Relation of therapy with tumour location and survival in 24 optic glioma cases

Mode of therapy	Intracranial			
	Intraorbital	Alive	Dead	Unknown
Orbitotomy*	8			
Biopsy + radiation†		3	4	3
Subtotal tumor resection and radiation‡		2	2	—
Total tumor resection + radiation†		1	1	—
Ventricular shunts‡		3		2

*Five patients underwent lateral orbitotomy (modified Krönlein), three patients underwent lateral and transfrontal orbitotomy.

†All patients received average 5500 rad radiotherapy and carmustine therapy.

‡Ventricular shunts were performed in five cases in addition to other therapy.

Table 6 Effect of therapy on prognosis for visual acuity in total of 14 survived optic glioma cases

Localisation	No. of patients	Visual acuity		
		Decreased	Stable	Increased
Orbital	8	8 (absolute)	—	—
Intracranial	6	—	6	—
Total	14	8	6	—

support this view, because approximately 71% of patients had symptoms and signs before 7 years of age.

Although exophthalmos is accepted as a favourable prognostic sign, indicating intraorbital localisation of the tumour, exophthalmos was present in 18.7% of our cases of intracranial tumours as compared with 20% of Chutorian and colleagues'¹⁰ cases. A mild degree of exophthalmos rarely exceeding 3 mm was reported in their series in contrast with our intra-orbital cases, in six of which we observed severe degrees of exophthalmos varying from 7 to 12 mm. In most of our cases of intraorbital gliomas the eyes were displaced inferonasally and inferotemporally, though Reese⁶ described straightforward displacement in mild degrees of exophthalmos.

In four of the six cases of prominent exophthalmos the histopathological examination revealed large cystoid spaces filled with alcian-blue-positive mucoid material, a finding that supports the idea of rapid enlargement of the tumour due to abundant accumulation of mucosubstance, as previously shown by Anderson and Spencer.³ Enormous amounts of mucosubstance within the tumour might account for a sudden increase in degree of exophthalmos in orbital gliomas as well as causing important functional disturbances in intracranial optic gliomas.

In the literature optic gliomas arising within the orbit adjacent to the eye globe are said to produce papilloedema in contrast to the optic atrophy associated with tumours located distal to the eye or intracranially.^{7,10} We failed to find any relationship between papilloedema and atrophy in accordance with tumour localisation in our study.

The relation between optic glioma and von Recklinghausen's disease has long been recognised. The incidence ranges from 10% to 30%.⁵ Lloyd⁷ found 40% of patients with optic glioma had stigmata of neurofibromatosis. We reported caf  au lait spots in six patients (25%) with optic glioma, which is in accordance with published reports. A 20-year-old girl who was found to have histopathologically confirmed intracranial neurofibroma, acoustic neurinoma, and neurinoma of the lumbar region besides optic glioma is a good example of the association of optic gliomas with other tumours as noted by Walsh and Hoyt.¹¹

We have observed a gratifying success in approaching progressive intraorbital gliomas by the Kr nlein operation described by Berke.¹⁴ No patient in our series had recurrence of the orbital tumour, which is in accordance with Tym's¹⁵ and Spencer's¹⁶ observations. Marejawa and colleagues¹⁷ reported recurrences of incompletely excised intraorbital and intracranial optic gliomas.

The best treatment of intracranial optic gliomas is still controversial—whether surgery, radiotherapy,

or both.^{7,10,18,19} We could not find any correlation with the mode of therapy and its effect on survival and visual acuity because of the small numbers of patients receiving different types of treatment.

A mean duration of eight years' follow-up in our own series showed a low survival rate of 37.5% in cases of intracranial optic glioma. Rush and colleagues²⁰ reported that 85% of patients with gliomas of the optic nerve or chiasm had survived a mean duration of 17 years, while 44% of the patients with chiasmal optic gliomas survived a mean duration of 19 years.

In conclusion, a follow-up study with a mean duration of eight years in our own series of 24 patients demonstrated that, though optic gliomas are accepted as benign hamartomatous tumours, they can have an aggressive course, affecting the chiasm and third ventricle and leading to a fatal outcome. The low survival rate as of 37.5% in our series might be taken as a good evidence of the aggressive nature of these tumours. As there are so many conflicting views on the therapy of optic nerve gliomas, the surgeon should evaluate each case individually. Patients should be examined at regular intervals, with special attention to visual acuity and neurological signs so that the best time and mode of therapy can be selected.

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New silicone tipped cannulas for subretinal fluid drainage

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SUMMARY Two new disposable cannulas for internal drainage of subretinal fluid are described in this article. We describe a curved and a straight version consisting of plastic hubs, 20 gauge proximal and 25 gauge distal stainless steel hypodermic tubing, and soft and flexible silicone tubing overmounts. Both these cannulas facilitate atraumatic drainage of subretinal fluid through pre-existing retinal holes and tears or through a retinotomy performed during vitreoretinal microsurgery.

Vitreoretinal microsurgery is routinely performed for the correction of complex retinal detachment, and there is an increasing trend of performing total intraocular treatment, including vitrectomy, fluid-gas exchange, and endophotocoagulation. To maintain this form of total intraocular treatment it is better to perform internal drainage of subretinal fluid than external drainage, which may often be difficult, cumbersome, and time consuming. Flynn *et al*¹ have developed a sophisticated cannulated extrusion needle for this purpose. However, this is an expensive and reusable device and can be used only in combination with a complex fluid-gas exchange machine. Flynn *et al*² have also described an inexpensive straight, silicone tipped extrusion cannula which can be fashioned by the surgeon prior to surgical use.

We have developed two separate cannulas, one straight, the other curved. Each cannula has a yellow, colour coded plastic hub attached to hypodermic stainless steel tubing. The metal tube is 28 mm long, with the 20 gauge proximal segment being 22 mm long and the distal 25 gauge segment being 6 mm. A medical grade silicone tube, 12 mm long, is mounted over the distal metal segment thus enabling a 'silicone only' protrusion of approximately 6 mm. The curved version has a distal segment radius of curvature of approximately 10 mm. The curvature is minimal and facilitates entry into holes or tears that are difficult to reach.

The cannulas are commercially manufactured and

therefore have consistent, smooth, well rounded edges, and securely mounted silicone tubing overmounts that will not inadvertently dislodge into the vitreous cavity or in the subretinal space during the drainage procedure. The external surface of the terminal segment of the metal cannula is vapour blasted to facilitate a secure friction fit of the silicone overmount.

The soft and extremely flexible silicone tip of either

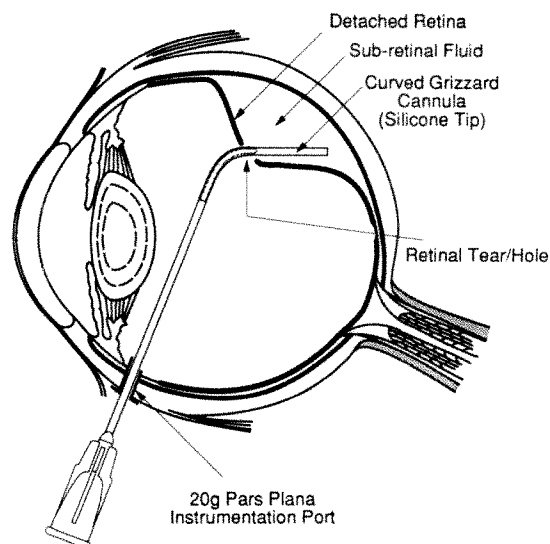


Fig. 1 Schematic depiction of curved cannula in use during internal drainage of subretinal fluid.

cannula can be inserted into an existing posterior or peripheral retinal break or hole and guided into the subretinal space (Fig. 1). These cannulas can similarly be used in situations where the surgeon needs to make a hole to facilitate internal drainage. The cannulas can be used by being attached to a flute handle or alternatively in conjunction with an automated suction device. The main shaft of both cannulas is 20 gauge and therefore can be inserted through a 20 gauge incision or instrumentation port. The straight cannula is ideal for posterior tears, and the curved design enables easier manipulation through peripheral tears. When the retinal hole or break is small, the silicone overmount can be removed to facilitate insertion of the 25 gauge distal

segment of the metal cannula through this small hole. The silicone tipped cannulas described in this article are available from Visitec Company, Sarasota, Florida, USA.

The authors have no financial interest in the cannulas described in this article.

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Choroidal malignant melanoma in an albino

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SUMMARY This is the first report of an amelanotic melanoma arising in the unpigmented choroid of a tyrosinase-positive oculocutaneous albino (TPOCA). Melanosomes within the tumour showed a maturation arrest in the unpigmented type II (premelanosome) phase. Other neural crest derived melanocytes in iris and choroid showed similar limited melanogenesis. The neuroectodermally derived melanocytes of the iris, ciliary body, and retinal pigment epithelium (RPE) contained mature melanosomes, though clinically the RPE was pale. The significance of this tumour arising in an albinotic eye is discussed.

Although cutaneous malignant melanomas are described in albinos,¹ ocular melanomas have not been reported. Oculocutaneous albinism has an incidence of 1 in 10 000 in the UK,² and the incidence of tyrosinase-negative and tyrosinase-positive albinism is roughly equal.³ Tyrosinase-positive oculocutaneous albinism (TPOCA) therefore probably has an incidence of 1 in 20 000. The incidence of choroidal melanoma is 2–6 per 10 000.⁴ The cumulative risk, if the two conditions are unrelated, should be at most 3 per 100 000 000, but may be as little as 1 per 100 000 000.

Case report

A 22-year-old Caucasian woman presented with a one-month history of painless loss of vision in her left eye. She was a tyrosinase-positive oculocutaneous albino and was born with white hair but had subsequently developed some pigmentation and was a light blond. Her best visual acuity had previously been 6/24 in each eye. She was in excellent health with no systemic symptoms on direct questioning. Both her sisters were albinos, and there was no other relevant family history.

On examination she had light blond hair with skin that did not tan in the sun. The irides were blue but translucent on retroillumination. The corrected

visual acuity was 6/24 in the right eye but hand movements in the left. Pendular nystagmus affecting both eyes had a rotatory element and was typical of that found in albinos. The fundi appeared non-pigmented, with an absent foveal reflex at the right posterior pole. At the posterior pole of her left eye a pale oval choroidal mass was situated beneath the macula (Fig. 1A). The tumour extended to, and obscured, the optic disc. It was globular and measured approximately 4 disc diameters at its longest axis. There were no drusen or orange pigment deposits on its surface. When the patient was upright, there was evidence of shifting fluid, with the retina detached inferiorly. No retinal holes were seen on examination of the retinal periphery.

Ultrasonography showed a solid mass which was sharply elevated, and though a collar stud appearance was not seen the configuration suggested a choroidal malignant melanoma that had burst through Bruch's membrane.

Fundus fluorescein angiography showed tumour vessels during dye transit (Fig. 1B) and hyperfluorescence of the mass in the later stages (Fig. 1C).

The patient was fully investigated for a primary neoplasm elsewhere in the body.

The clinical appearance was more suggestive of an amelanotic melanoma than a choroidal metastasis or haemangioma, and this was the consensus of several ophthalmologists. During the two weeks following presentation the retina became totally detached, and the eye was enucleated. It was immediately placed in paraformaldehyde fixative for electron microscopy.

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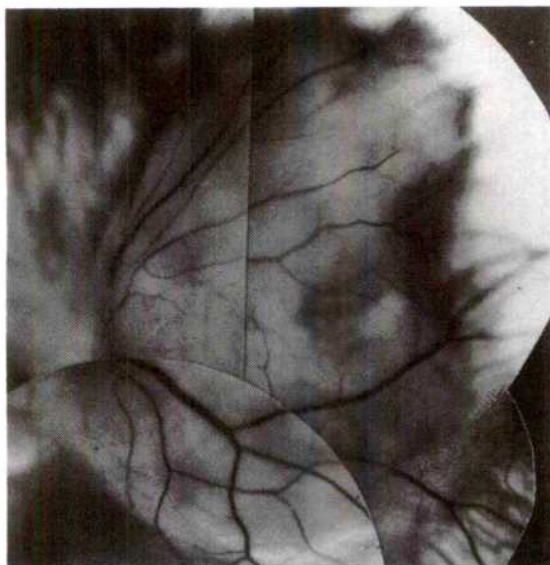


Fig. 1A

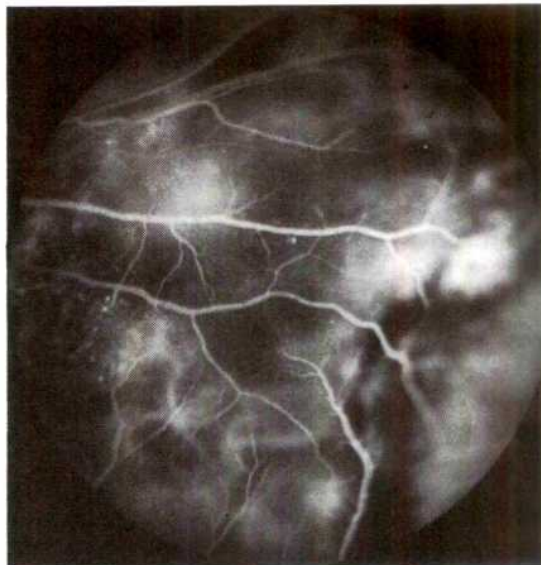


Fig. 1B

Fig. 1 A: Choroidal malignant melanoma at the posterior pole of the left eye. B: With tumour vessels demonstrated during fluorescein transit. C: Hyperfluorescence of the tumour in the late stages of the study.

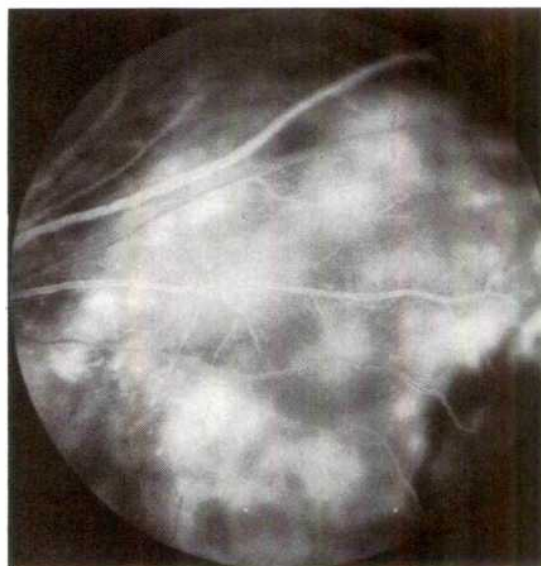


Fig. 1C

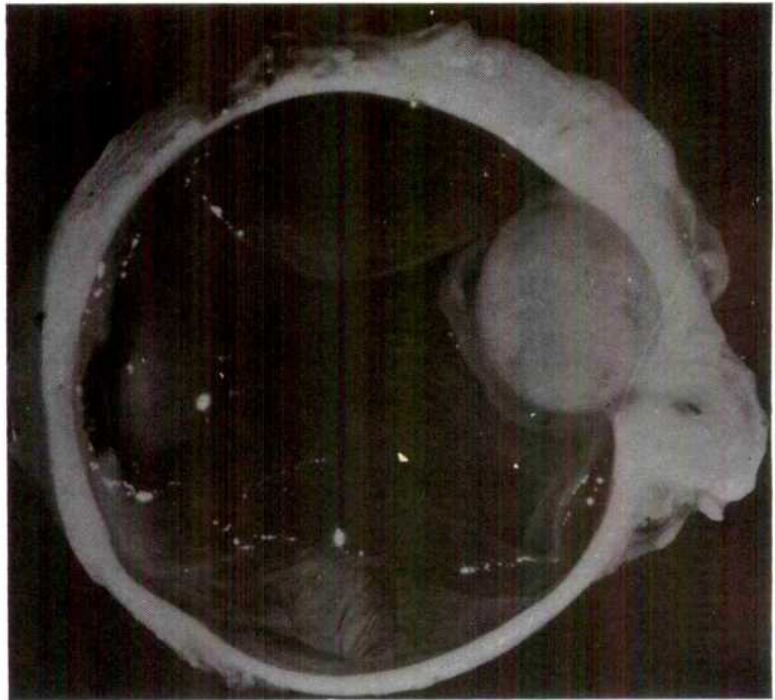
The indications for radical approach were the juxta-papillary situation of the tumour and the presence of total serous retinal detachment. To improve her cosmetic appearance the extraocular muscles were sutured to an implant. This resulted in nystagmoid movements being transferred to her prosthesis.

PATHOLOGY

The eye had a pale blue-grey iris, and when it was

opened pigmentation of the posterior iris pigment epithelium (IPE) and ciliary body was seen. The retinal pigment epithelium (RPE) was very lightly pigmented macroscopically, but the choroid and the cut surface of the iris stroma were white, showing no evidence of melanisation. This was confirmed microscopically where the iris stromal and anterior border cells border and the choroid were unpigmented. Samples were taken from the iris stroma and

Fig. 2 Gross specimen with an amelanotic choroidal mass at the posterior pole.



epithelium, RPE, and choroid for electron microscopy.

There was a pale tumour, 6.5 mm in diameter (Fig. 2), with a rounded outline, arising in the superotemporal posterior fundus, overlapping the optic disc, associated with a large, almost complete serous detachment of the neural retina. The tumour was sampled for light and electron microscopy, and whole-eye sections were also prepared.

On microscopy the solid choroidal tumour had prolapsed over part of the optic disc and had focally ruptured Bruch's membrane (an event which would have eventually led to a collar stud configuration had the tumour continued to grow). No extrascleral or scleral extension of the tumour was seen. The spindle cells of the tumour were arranged in fascicles and in some areas were arranged in a pseudoadenomatous pattern. The appearances were not, however, those of a metastatic adenocarcinoma or carcinoid tumour, as had been suggested in the clinical differential diagnosis, nor was there any palisading of nuclei or foci of myxoid degeneration typical of a schwannoma, which might be included in the differential diagnosis of a spindle cell tumour of the choroid.

The appearances were those of an amelanotic melanoma, with a predominance of spindle B cells with plump nuclei and prominent red nucleoli (Fig. 3). More compressed spindle A cells with

elongated nuclei were seen at the periphery, pressed against the sclera. Reticulin was found on special staining, but there was no evidence of an epithelioid cell population. In view of the lack of clinical,

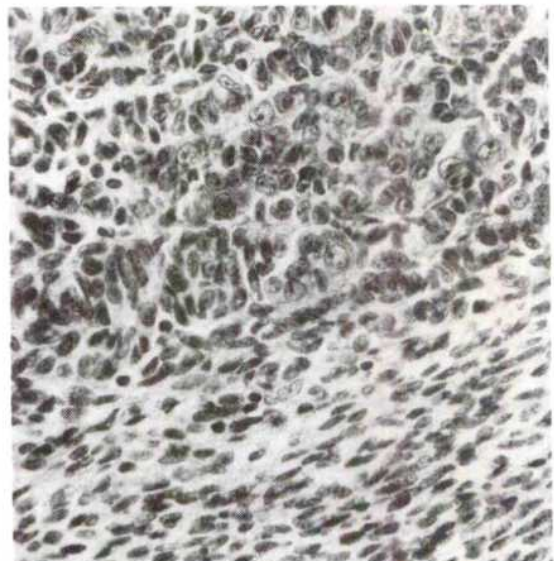


Fig. 3 Fasciculated pattern of spindle cells in amelanotic malignant melanoma. ($\times 350$).

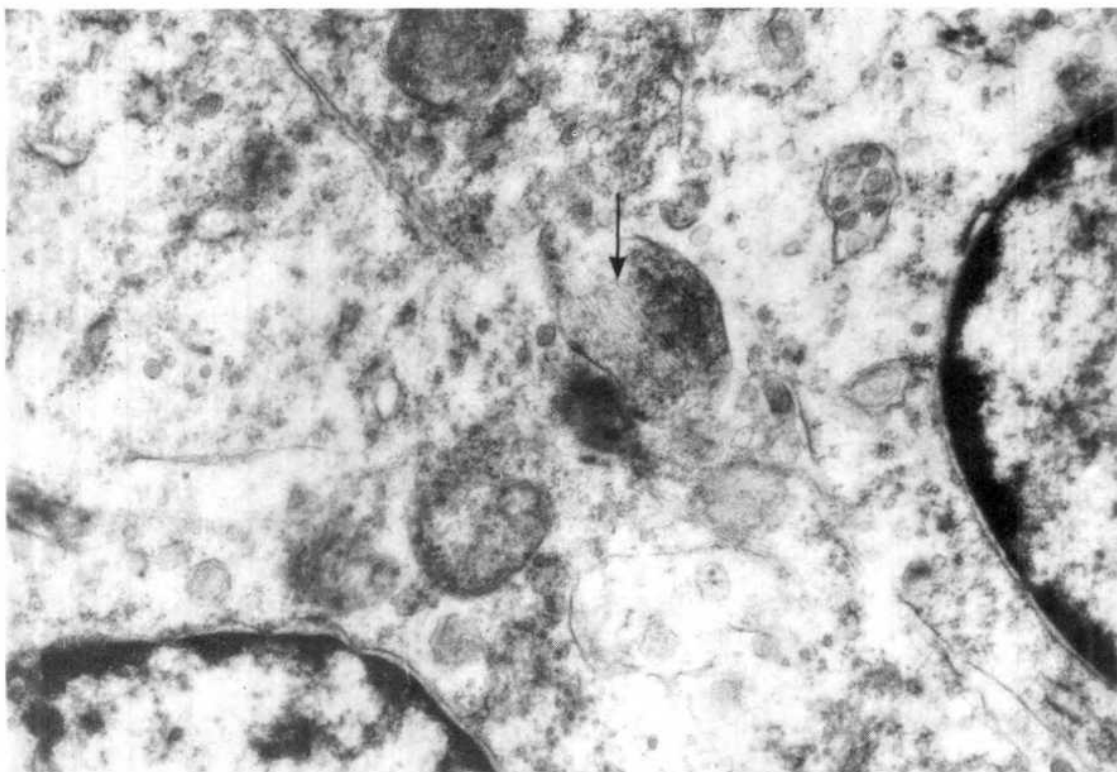


Fig. 4. Stage II premelanosomes in tumour cell cytoplasm (arrow). ($\times 29\,000$).

macroscopic, and microscopic pigmentation the failure to demonstrate melanin with conventional stains such as Schmorl and bleach, and Masson-Fontana was perhaps not surprising. Electron microscopy clinched the diagnosis by demonstrating immature and atypical melanosomes typical of amelanotic melanomas.⁶ A few type II⁶ melanosomes (premelanosomes) were visible, as well as more abortive vesicular organelles. These immature melanosomes were demonstrable in both types of spindle cells, but more atypical forms were commoner in the spindle B cells. No maturation to type III and IV melanosomes was visible in the tumour and most melanosomes were rather poorly formed (Fig. 4). No dense core vesicles (consistent with carcinoid tumours) or L use type bodies, more typical of schwannomas, were present. Immunohistochemical studies were subsequently performed, though fixation in paraformaldehyde was not optimal. S100 protein was demonstrable in the tumour, especially at the periphery, in the choroid in dendritic cells, and in the cellular iris stroma. These findings were consistent with a neural crest origin. S100 protein was also found within perivascular glia

of the nerve fibre layer in the detached retina. Similarly the Warthin-Starry-DOPA reaction⁷ was also performed and showed a small amount of silver staining only just demonstrable at light level but more certainly at electron microscopic level, where an argyrophil reaction highlights the DOPA-reactive immature melanosomes.

Since reports of albinotic eyes are still rare,^{8,9} electron microscopy was performed on other parts of this enucleated eye. Despite the clinical translucence of the iris and the pallor of the fundus, some pigmentation had developed in the epithelia of the iris (IPE) (Fig. 5) and ciliary body and to a less extent in the RPE. This pigment was visible macroscopically and with the light microscope, and it stained as melanin with the traditional techniques (Schmorl and Masson Fontana). On electron microscopy type III and some type IV melanosomes were seen in these melanocytes. Type IV melanosomes were demonstrable in the RPE, albeit in fewer numbers than in some fundi, especially at the apices of the cells, and an osmication–non-osmication technique confirmed that these electron dense organelles were not all lipofuscin, generated after phagocytosis of rod outer

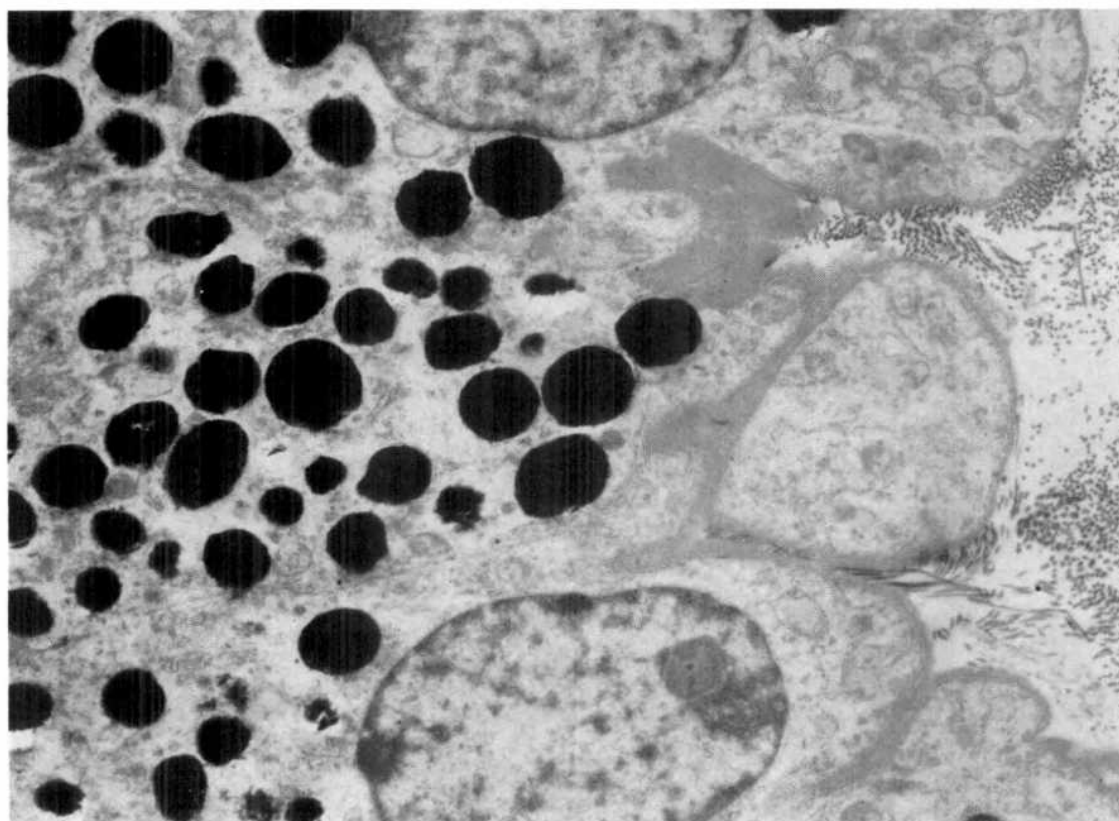


Fig. 5 Normal type IV melanosomes in iris pigment epithelium. ($\times 8400$).

segments. Such a potential confusion of organelles is less likely to occur in IPE (Fig. 5) and ciliary body, and again maturation of melanogenesis had occurred, with type IV melanosomes present.

Immature melanogenesis, to the same stage (type II) as the tumour, had occurred in the iris stromal and anterior border melanocytes and in the choroidal melanocytes. No type III or type IV organelles were seen.

Discussion

If the incidence of choroidal melanoma is 2-6 per 10000 and the theoretical incidence in tyrosinase-positive albinos is 3 per 100000 at most, then it is unlikely with a confirmed incidence of 1-3 per 100000000 that the two conditions will be reported together, especially as there is underdiagnosis of TPOCA in the Caucasian population, with a high incidence of blonds. Foveal hypoplastic abnormalities,¹⁰ indicative of abnormal decussation of the optic pathways, coupled with nystagmus are the most selective diagnostic criteria.

Choroidal melanomas are said to be commoner in people with pale irides and the increased incidence may be associated with exposure, especially intermittent exposure, to ultraviolet irradiation.¹¹ Pale irides are less able to block sunlight than dark ones, and circumstantial evidence, such as the higher incidence of inferior pole melanomas, where the greatest incidence of unblocked light might impinge, and the relative paucity of melanomas in brown eyed people would seem to support this hypothesis. Therefore one might expect albinos with iris translucence to have a higher incidence of melanomas than blonds with blue or grey irises.

TPOCA patients do slowly develop darker irides than they are born with, as there is selective melanogenesis in the neural crest derived melanocytes of hair, skin, and iris stroma.⁹ However, most albinos are photophobic and many wear eye protection, a factor previously examined and associated with less frequent use among cases of melanoma than controls.¹¹ Most of the damage from incident UV light is thought to occur through the immature (non-adult) lens, which does not screen it out.¹² Albino children are probably less

likely to be sun worshippers than their more pigmented peers.

It is interesting to note that this girl had no evidence of maturing melanisation in her iris stroma or choroid (and did not tan) and that a similar phase of maturation arrest was apparent in her tumour, also derived from neural crest melanocytes. She had more mature pigmentation in the pigment epithelia, where melanogenesis is usually complete at birth after starting at five weeks' gestation in normal people. Her neuroectodermally derived melanocytes had developed along normal lines, despite there appearing to be more type III melanosomes than usual and fewer type IV, though both were present in all three epithelia. The development of a weak positive argyrophilic response when the 'double labelled' Warthin-Starry-DOPA technique was used indicates that in this TPOCA patient the tumour could precipitate silver even though it was amelanotic. This is analogous to the positive hair-bulb incubation test technique where tyrosine is utilised if presented to the melanocytes in TPOCA patients' hairs, and darkening occurs.

This paper illustrates what may be a chance occurrence of two relatively uncommon conditions occurring together, but further reports should be expected if there is a non-random association.

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Uveal lymphoid infiltrates: immunohistochemical evidence for a lymphoid neoplasia

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SUMMARY A 67-year-old man presented with a diffuse choroidal and ciliary body infiltrate, suggesting clinically and ultrasonographically a diffuse uveal melanoma. After enucleation both morphological and immunohistochemical data were highly suggestive of a diffuse, low-grade B cell lymphoma or lymphoplasmacytic immunocytoma. The difficulties of clinical and histopathological differential diagnosis of uveal lymphoid infiltrates are emphasised. In view of the excellent life prognosis of these tumours, treatment of the patient should be directed towards the preservation of ocular function.

Until recently most cases of uveal lymphoproliferation have been diagnosed from histopathological examination.¹⁻³ This condition, currently designated as 'reactive lymphoid hyperplasia,' was considered benign until recent immunological techniques raised the suspicion of a low-grade lymphomatous proliferation.^{4,5}

We report a clinicopathological study of a case of diffuse, unilateral, uveal lymphoproliferative disease in which both morphological and immunological patterns strongly suggested the diagnosis of small lymphocytic lymphoma with a plasmacytoid differentiation.

Case report

A 67-year-old man was seen on 5 October, 1986 complaining of seeing shadows in front of his right eye and changing refractive status for six months. Past medical history was negative.

Corrected visual acuity was 20/60 OD, 20/20 OS. In the right eye slit-lamp examination showed scleral thinning over a dark mass, 2 mm posterior to the nasal limbus. Transillumination disclosed the presence of a ring mass. The anterior segment and

vitreous appeared normal. Fundus examination revealed a ciliary and a subretinal mass extending to the neighbourhood of the temporal arcades, with a shallow subretinal detachment. Ultrasound disclosed a diffuse tumour largest at the ciliary body level. The mass showed low internal reflectivity, with a suspicion of intrascleral infiltration nasally. No choroidal excavation was seen (Fig. 1). No extraocular tumour was detected. CT scan of the brain, globes, and orbits showed a diffuse mass in the right globe (Fig. 2).

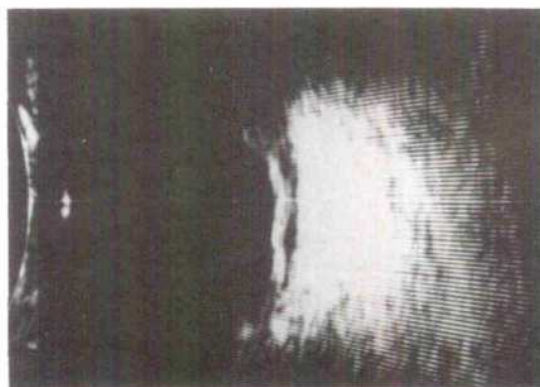


Fig. 1 Echogram B: diffuse tumour with low internal reflectivity.

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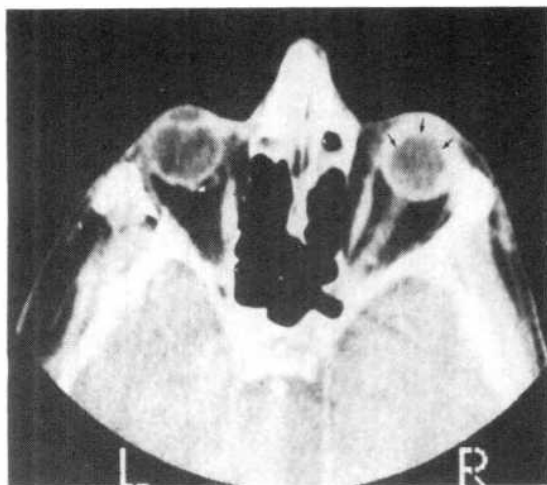


Fig. 2 CT scan: Diffuse involvement of the choroid and parts of orbit and optic nerve. Arrows indicate tumour.

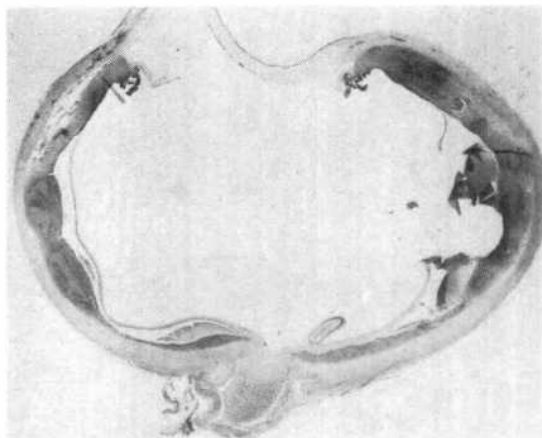


Fig. 3 Whole amount of eye showing diffuse involvement of choroid and ciliary body by a lymphoid proliferation. The retina is part detached. (H and E, $\times 1.5$).

Ancillary laboratory tests were negative, including spleen and liver scans, biochemical blood tests, blood cell counts, and protein electrophoresis. Quantitative immunoelectrophoresis showed only elevated IgM 4370 mg/l (normal 650-2800).

Three months later the suspected uveal melanoma progressed toward the posterior pole with retinal detachment and a drop of visual acuity in the right eye to 20/300. Enucleation was performed on 14 December, 1986.

In view of the histopathological findings a bone marrow aspirate was performed. This provided no evidence for a marrow involvement by lymphoma.

HISTOPATHOLOGY

The choroid and the ciliary body were extensively infiltrated by a lymphoid proliferation (Fig. 3). No extraocular extension was seen on serial sections. The infiltrate was focally follicular, with reactive-appearing follicles containing transformed lymphocytes, numerous mitoses, and phagocytic macrophages (Fig. 4). In the interfollicular regions there were diffusely infiltrating lymphocytes and plasma cells with no cytological abnormality (Fig. 5). A few plasmacytoid cells contained intranuclear periodic acid Schiff positive inclusions (Dutcher bodies) (Fig. 6).

The retina was partially detached, with an eosinophilic subretinal exudate. No optic nerve, retinal, or extraocular involvement was seen.

Immunoperoxidase staining with monoclonal antibodies to human immunoglobulin heavy and light chains were carried out on paraffin embedded sections with an avidin biotin peroxidase conjugate

(Vector Laboratories, California). Plasma cells, plasmacytoid cells, and Dutcher bodies within and around the follicles showed a marked predominance of cytoplasmic IgM staining. Only scattered λ and IgG positive cells were present (Fig. 7 A-C).

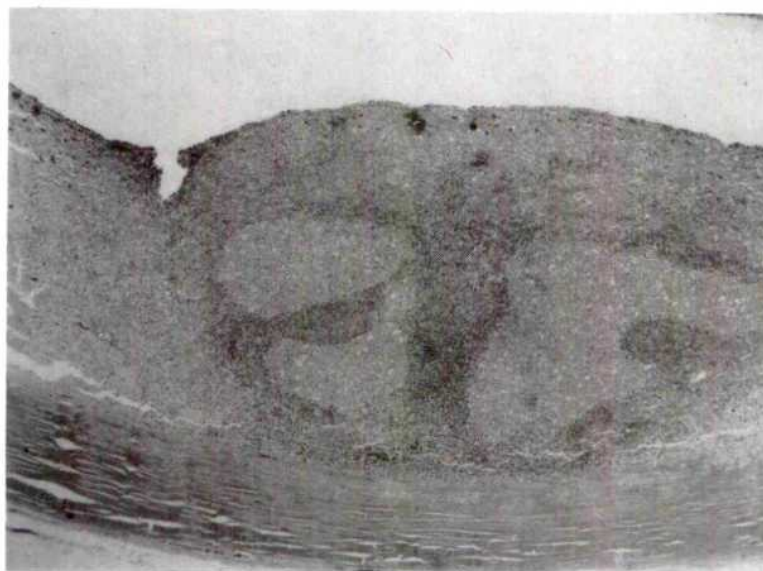
Transmission electron microscopy studies were performed from the paraffin blocks. In the germinal centres macrophages, plasma cells, and small lymphocytes were seen, a finding consistent with the light microscopic finding of polymorphism. In addition some plasmacytoid cells showed cytoplasmic disorganisation, characterised by eccentrically located cytoplasmic organelles like those found by Knowles and Jakobiec in their group IV lymphomas⁵ (Fig. 8).

The diagnosis of small lymphocytic lymphoma with plasmacytoid differentiation was made, or lymphoplasmacytic immunocytoma.⁶

Discussion

Uveal lymphoid infiltrates (ULI) (so-called lymphoid hyperplasia) present difficulties in differential diagnosis from diffuse uveal melanoma. Except for two reports,^{2,5} in most cases of ULI the diagnosis was first established after enucleation or, in one instance, through a biopsy of the ciliary body.^{1,2,7-9} The age distributions of the patients and most symptoms are similar in ULI and diffuse uveal melanoma.¹ The diagnosis of lymphoid infiltrates should be suspected at an early stage if creamy choroidal infiltrates with indistinct edges, unassociated with retinal detachment or alteration of the retinal pigment epithelium are present.¹ Other suggestive features include

Fig. 4 A partially follicular pattern is evident. The follicles are irregular, sharply demarcated, and have a 'starry sky' pattern, similar to reactive germinal centres. (H and E, $\times 27$).

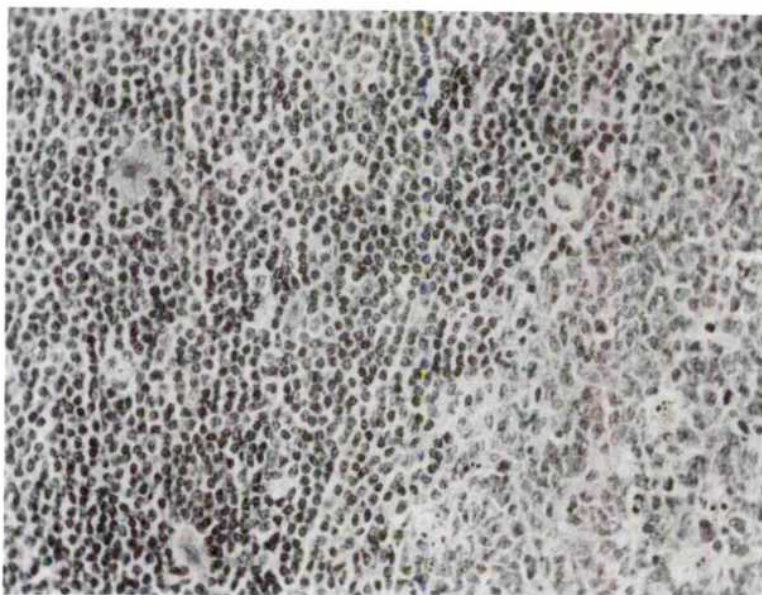


associated extraocular foci, glaucoma (66%), inflammatory signs (56%), or bilateral involvement (10%).¹ Desroches *et al*,² and Jakobiec *et al*³ emphasise the value of ultrasound findings: low internal reflectivity, lack of vascular pulsation, absence of choroidal excavations, integrity of the sclera. Jakobiec *et al* were able to reach the diagnosis through a biopsy of extraocular lesions.³ In our case, owing to the lack of clinical, ultrasonographic, and biological distinctive

features, a differential diagnosis of reactive lymphoid hyperplasia seemed unlikely.

ULI present a problem in histological diagnosis. The first reported cases were identified as lymphosarcomas; Zimmermann reclassified them as reactive lymphoid processes.⁷ In 1972 Ryan *et al*⁸ reviewed 21 cases and described the classical histological pattern of what they called 'reactive lymphoid hyperplasia of the uvea.'

Fig. 5 Higher magnification of follicle and interfollicular region, showing reactive-appearing follicle. Interfollicular cells are predominantly small lymphocytes. (H and E, $\times 270$).



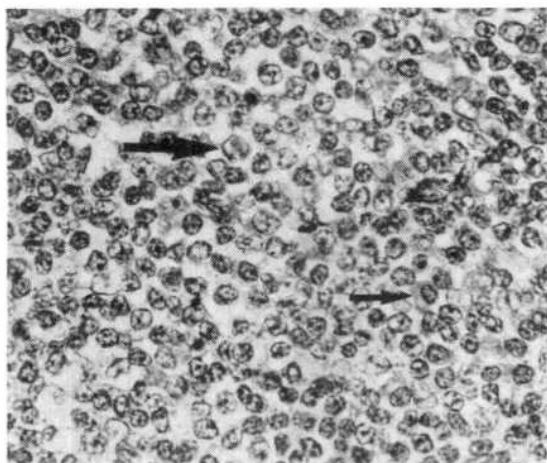


Fig. 6 The infiltrate contains a mixture of small lymphocytes and plasma cells (small arrow). Some cells have intranuclear PAS-positive inclusions (Dutcher bodies, large arrow). (PAS, $\times 450$).

Yet the reservations held by all the authors on the purely morphological identification of extranodal lymphoproliferative diseases apply to the uvea as well. These doubts stem from (1) the lack of architectural features usually present in lymph nodes,

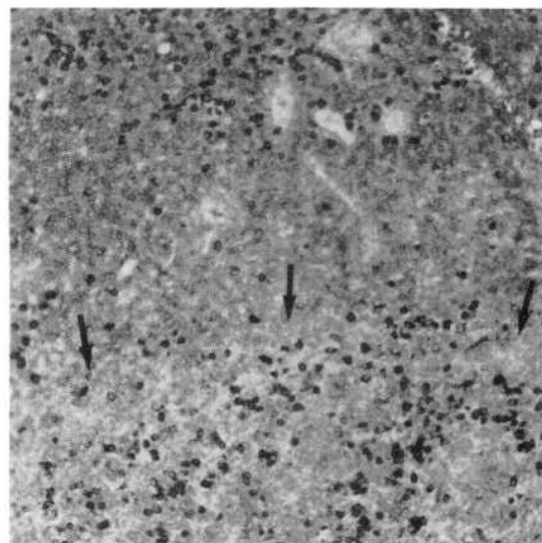


Fig. 7A Immunoperoxidase stains on paraffin-embedded sections. A ($\times 100$): Antibody to κ light chain shows cytoplasmic staining of cells within the follicle centre (arrows), and in the intermacular region, particularly the choriocapillaries (top). B ($\times 100$): Antibody to λ light chain (same field) shows only rare positive cells. C ($\times 280$): Antibody to μ heavy chain is similar to κ ; occasional Dutcher bodies stain positively (arrow).

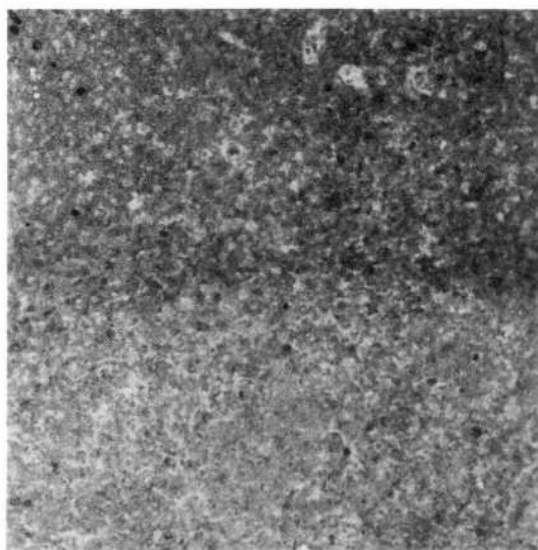


Fig. 7B

and (2) uncertainty as to the significance of germinal centres, Dutcher bodies, and plasma cells.^(10,11)

The diagnosis of lymphoma in extranodal lymphoid infiltrates that lack cytological abnormalities is a major problem in pathology.⁽¹⁰⁻¹⁴⁾ Immunohistochemical studies have thrown light on this question. Reactive infiltrates contain a mixture of cells with both α and λ immunoglobulin light chains

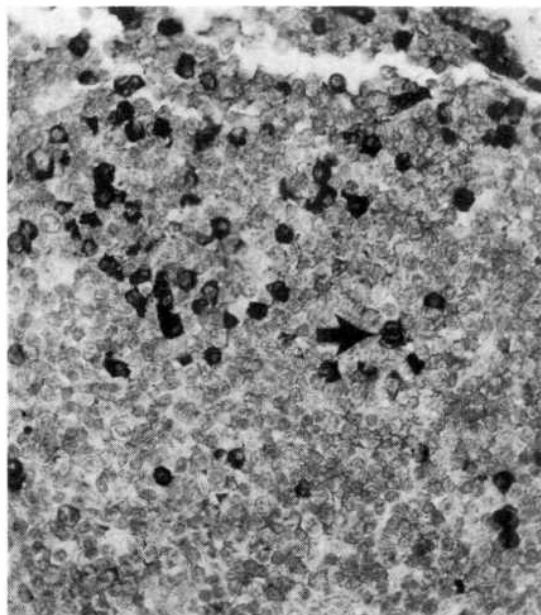
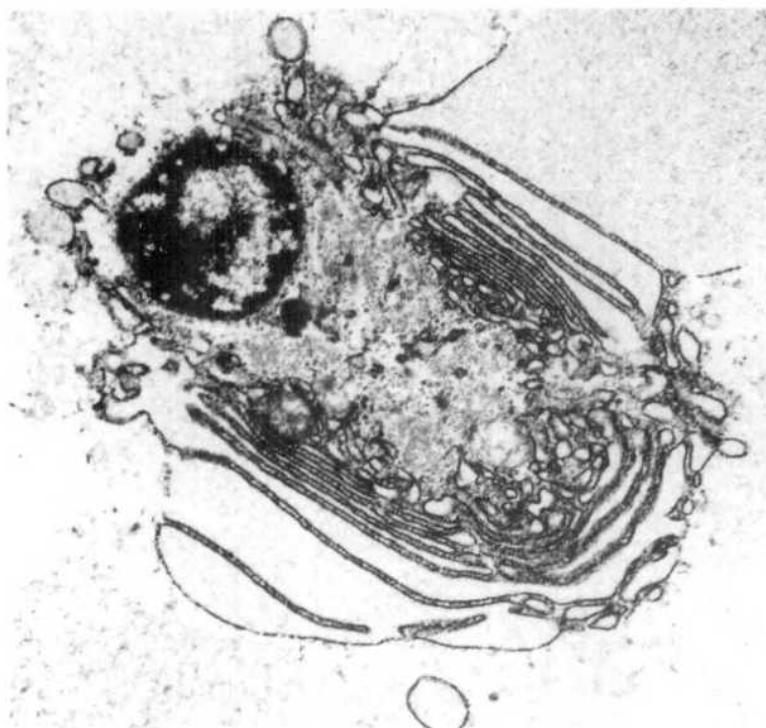


Fig. 7C

Fig. 8 Transmission electron micrograph: plasma cell with eccentric organelles (see text). ($\times 11\,800$).



(polyclonal), while neoplasms consist of cells expressing only one light chain – κ or λ (monoclonal). The application of this technique to extranodal lymphoid infiltrates, particularly in the orbit, has shown that most lesions previously diagnosed as pseudolymphoma are monoclonal B lymphocyte proliferations^{10–11, 13–15} – that is, low-grade B cell lymphomas.

These observations can now be applied to uveal lymphocytic infiltrates. Mauriello *et al*⁴ reported that in a series of cases of ULI studied by the immunoperoxidase technique the majority could be reclassified as well differentiated lymphoplasmocytic lymphomas. Histopathological examination of extraocular lesions in Jakobiec and colleagues' series provided morphological arguments for a lymphoid neoplasia.³ These tumours have a good prognosis for life, as has been reported for similar lesions occurring in the orbit.^{13–14, 16} Systemic involvement is rare.⁴

Consequently the accurate classification of these lesions as benign or malignant, which remains difficult, approaches an academic rather than practical consideration. The patients must be continually followed up for systemic disease. In its absence, the management of low-grade uveal lymphomas should be directed to the preservation of ocular function. Low-grade lymphomas of the conjunctiva and the ocular adnexa respond well to

doses of radiation therapy that preserve visual function.¹⁷ High-grade lymphomas of the uveal tract have been successfully treated by radiotherapy.¹⁸ We therefore advocate the use of corticosteroids as a diagnostic tool,² followed by an associated low-dose irradiation if the diagnosis is very likely.

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Correspondence

Retinal burns from MIG-welding arcs

SIR, I read the article by G P H Brittain¹ on retinal burns caused by exposure to MIG-welding arcs with great interest. I had not seen any cases in Australia and so I was very interested to study the illustrations. Two cases were described. The first case was illustrated in Fig. 2 but I could not see the 'small dark lesion above each fovea' said to be present. The second case is illustrated in Figs. 3 and 4, and I felt the appearances were more consistent with a retinal pigment epithelial detachment than a photocoagulation burn.

Mr Brittain also claims that the lesions in the right and left eye are symmetrical and illustrate the principle of physiological diplopia. On looking at Fig. 4, however, there were two very obvious lesions in the right eye with a larger one below the horizontal meridian and lateral to the fovea. In the left eye only a large lesion is clearly visible, and it is above the horizontal meridian. On this evidence the lesions in the right and left eyes are not symmetrical. I think we should always be alert to the possibility of retinal damage in people who use arc welders and are not properly protected. I am not convinced, however, that Mr Brittain's article has given us illustrations of retinal burns that have been caused by exposure to MIG-welding arcs.

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Reference

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SIR, I would like to answer the criticisms against my report of two cases of retinal burns caused by exposure to MIG-welding arcs made by Mr Beaumont, who has not seen any such cases in Australia and remains unconvinced by my article.

I must agree with his first criticism that the black-and-white illustrations in Fig. 2 do not make the small parafoveal lesions obvious. I had included them for the sake of completeness, but I accept that while the lesions are poorly visible in the original colour transparencies they have virtually been lost in the black-and-white illustrations made from them. The lesions were seen and noted by several of the ophthalmic staff at the Leicester Royal Infirmary. Because of the poor contrast difference between the lesions and the background retina they were very difficult to photograph with standard high intensity flash photography.

Mr Beaumont feels that the appearance of the lesions in the second case is more consistent with retinal pigment epithelial detachments than with photocoagulation burns. I agree that the lesions are at this retinal level where pigmentation and therefore thermal effects of light absorption are maximal. The lesions, however, were not elevated as RPE detachments would be. There was no focal point of

fluorescein leakage nor 'smokestack' sign, and the lesions showed no sign of enlargement with time, though they did take up dye as would any traumatised tissue. In both cases the lesions tended to resolve in the few days subsequent to exposure to the arc, implying that they were not spontaneous events but caused by the arc.

I would ask him to refer to the original description of the gross and microscopic changes induced by the laser beam in human eyes by Zweng *et al.*¹ in particular to examine their illustration (Fig. 4) which shows a photograph of experimental laser photocoagulation burns at 28 hours (a similar period elapsed between exposure and photography in my second case). In their words 'the lesions consisted of a central depigmented area surrounded by a rim of increased pigmentation which in turn was surrounded by a halo of depigmentation.' This is also an accurate description of the lesions in my second case.

He does not feel that the lesions in the second case are symmetrical, though both major lesions lie centred 1.2 disc diameters from the fovea and are very similar in shape and size. The major lesion in each eye lies one above and one below the horizontal meridian because the head was tilted to the right as the patient lay on the ground to reach under the car. Although oblique, the position of these lesions is symmetric about the fovea and certainly could be explained by the principle of physiological diplopia as I have suggested. The smaller lesion in the right eye could have occurred at another exposure while the left eye was closed or protected by the visor and in no way detracts from the symmetry of the other lesions.

I am convinced that in both cases I reported the lesions resulted from exposure to MIG-welding arcs. I do not wish to imply that such injuries are common. The circumstances in which these retinal injuries occurred may have been exceptional in that the first was caused by prolonged exposure, and the second by brief but very intense exposure due to the close proximity of the arc to the patient's dilated pupils. In neither case did there appear to be any persistent visual symptoms, and it is possible that such injuries go unobserved, overshadowed by the more immediate problem of an acutely painful ultraviolet keratitis. There may be long term problems resulting from exposure to such high intensity light, and I feel that MIG-welding arcs should be treated with a great deal more respect than they are presently afforded.

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Reference

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Precision versus confusion

SIR, I read with interest 'Why should surgery for early-onset strabismus be postponed?' by M Deller.¹ Dr Deller is to be congratulated on his careful studies of this condition, which

lend further and important support to its prompt treatment for best results. His long term follow-up is especially commendable and encouraging.

I would protest, however, against the continued and further abuse of the English language in descriptions of the surgery for this condition, which have now finally reached the point of miscommunication and erroneous meaning, to wit: In the first line of the summary what is or are the 'bilateral rectus muscles'? Later in line 6 of the summary the author talks further about 'bimedial rectus recession'. Further in the text he does state that what he is doing is as suspected: 'surgery is always symmetrical on the two medial recti, consisting of muscle recession . . .' We know then that what he is doing is what should be and has been properly described for many years as 'bilateral medial rectus recession'. This has been, unfortunately, shortened in the last decade by many authors to 'bimedial recession' or 'bimedial rectus recession'.

It is the history of language that man will violate spelling and grammar rules to save time and for greater efficiency. Our language is full of such contractions and abbreviations. Sometimes, however, such contractions are inappropriate or imperfect, and confusion results along with the saving of time and energy.

Such is the case here, for one should immediately realise that the use of the term 'bimedial' in this context destroys the standard medical meaning of its opposite term, 'bilateral'. No clearer case or example of this confusion has been printed in our literature, to my knowledge, than in the summary of this article, which starts off with the term 'bilateral rectus muscles'. This is the final end product of the wayward process of contraction.

Whatever then is this? If one accepts that a 'bimedial rectus recession' is short for a 'bilateral medial rectus recession', then 'bilateral rectus muscles' must mean 'bilateral lateral rectus muscles'. But can we arrive at this conclusion only by inference, because we know about this condition and we know what the author is trying to say? We cannot understand this by what he has actually said, because there is no such entity as 'bilateral rectus muscles'.

The situation is hardly lost or desperate. The language has suffered this sort of abuse before, and has survived. It has, however, developed some defences against the confusion which can result in these situations. When two words are contracted into one, the convention is to use a hyphen if nothing is left out, and to use an apostrophe if something is left out, as in the word 'can't', a contraction of two words, 'can not'. Another example is 'isn't', a contraction for 'is not'. So, technically, Dr Deller and others should be describing this as a '*bi-medial rectus recession*'. The operation which is usually performed for exodeviations, a 'bilateral lateral rectus recession', would then be a '*bi-lateral rectus recession*'.

But the apostrophe is not, to me, sufficiently strong for what has been left out. It is not just a letter or two which has been dropped. Rather, a whole 'side' has been dropped ('lateral'), and the apostrophe, though it is most correct, doesn't seem strong enough.

We have therefore used the hyphen, which though not entirely appropriate is strong enough to get even the casual reader's attention to the fact that something unusual and significant is going on here²—that is, *bi-medial recession* or

bi-lateral recession. We would like to encourage others to do likewise, or if they have a better idea, let us hear it.

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PS Dr Deller does seem to appreciate precise words. He is to be commended for the use of the term 'retroequatorial myopexy'. His precision here makes the imprecision of his other terms, however, that much less understandable. Rather than 'alphabetical syndromes' he might prefer a word which seems to be gaining increasing use to describe these problems: 'anisotropia'.

SIR, I thank Dr Romano for his letter, which might otherwise be called a lengthy study on the hyphen—to be or not to be?

The terms 'bi-medial' or 'bimedial'^{2,3} as used by my British orthoptist-translator, are widely used by respected authors of English ophthalmic literature. Any misunderstanding of the fellow 'bi-with-or-without-hyphen lateral' is regrettable, as I share Dr Romano's desire to render as comprehensible as possible our scientific communication. I therefore cannot condone his—albeit ironic—proposition of the term 'anisotropia', with which he obviously relishes the prospect of creating a further opportunity to comment on confusion and inefficiency.

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Book reviews

Systemic Inflammatory Disease and the Eye. By W J DINNING. Pp. 247. £30.00. Butterworth: Guildford. 1987.

This small book is written at the interface of ophthalmology and general medicine. The opening chapter, on the signs of ocular inflammation, is followed by six chapters describing the various systemic diseases which may be associated with ocular inflammation as part of their multisystem involvement. It is important to realise that the book takes ocular inflammation in its widest definition and is not merely a

catalogue of uveitic syndromes; it includes, for example, diseases such as polychondritis and Sjögren's syndrome. Its approach is disease orientated, so that scleritis is, for example, discussed mainly under rheumatoid arthritis and alluded to elsewhere rather than discussed in its own right as an ophthalmic entity.

The chapters are headed sarcoidosis, systemic vasculitis syndromes, systemic lupus erythematosus, eye and joint disease, psoriasis polychondritis and bowel disease (a slightly odd grouping), and finally infectious disease and the eye. There is a rather uneven emphasis on some conditions. There are, for instance, 16 pages on sarcoidosis, 10 on SLE, and only half a page on AIDS. The general arrangement is to describe the systemic features and the type of ocular involvement with notes on the aetiology, diagnosis and, briefly, treatment, with short descriptions on immunopathology and aetiology—which I found the most interesting. Each chapter is very well referenced and illustrated with black-and-white photographs, many of which are unfortunately rather poorly reproduced.

Books such as this have a difficult role, for they often fail to satisfy either ophthalmologists or general physicians because the volume of material to be covered is so large. For instance, most ophthalmologists will want to dispense with the first chapter on ocular signs, though it may be of interest to physicians, and vice versa the same may apply to some of the medicine. The ratio of general medicine to ophthalmology on each topic varies considerably but is probably in the ratio of two-thirds medicine to one-third ophthalmology. I found, not surprisingly, that the ophthalmology was better done.

Ophthalmologists may use the book as a short handbook but will want to turn to the larger textbooks for more complete descriptions of systemic diseases or the conventional ophthalmic specialist texts for a fuller discussion of complications and treatment. It does, however, contain much easily readable information and will certainly find a role for quick and easy reference. It is a pity that the publishers did not do a better job on the presentation of the material for their author.

D J SPALTON

Ophthalmic Echography. Proceedings of the 10th SIDUO Congress. Edited by K C OSSOINIG. Pp. 625. £95.50. Kluwer: Dordrecht, Netherlands. 1987.

This book presents the proceedings of a congress held in 1984, but the contributions have been adapted for publication in 1987. It contains 103 papers drawn from 16 countries and is divided into three parts. The first part is dedicated to biometric ultrasound; the second and third parts deal with diagnostic ultrasound in intraocular and orbital and peri-orbital disease, respectively.

Some worthwhile papers dealing with axial length measurement and intraocular lens implant power calculation, corneal thickness measurement, and retinal/choroidal/scleral thickness measurement are presented in part 1. Fortunately there appears to be a heightened awareness by some authors that the major source of error in axial length measurement is misalignment of the probe. Fourier analysis techniques are used by several authors in the measurement of retinal/choroidal/scleral thickness, and there is a

refreshing recognition that echoes detected on A or B mode do not necessarily correspond to the boundaries of these interfaces.

Part 2, dealing with intraocular diagnosis, contains a mixture of the well known and the controversial peppered with some interesting and worthwhile observations despite many very poor greyscale/bistable displays. One paper claims A mode is useful in the differentiation of spindle cell and epithelioid malignant melanoma, an observation which is contradicted by the following paper. Other papers look at the response of malignant melanoma to radiotherapy. Some describe doppler techniques, but surprisingly duplex imaging (combined simultaneous doppler and real-time B mode) in ophthalmology is mentioned but not used or referenced in this context. Colour doppler imaging is not mentioned.

A series of papers on orbital disease are to be found in the final part of the book. Some interesting observations and useful measurements are presented in some papers. In the concluding appendix, dealing with the therapeutic use of ultrasound in choroidal detachment, which is recommended to us by the authors, there is some confusion whether three patients or 42 patients received this ultrasonic treatment.

This book will be of interest to those actively engaged in the field of ophthalmic ultrasound but at £95.50 is unlikely to appeal to those on NHS salaries.

MARIE RESTORI

Proceedings of the Retina Research Foundation Symposium. Vol 1. Edited by DOMINIC MAN-KIT LAM. Pp. 220. US\$ 24.95. Portfolio Publishing Company: The Woodlands, Texas. 1988.

Normally the published proceedings of symposia are among the most frustrating volumes presented to the scientific community. For those who attended the symposium they are sometimes helpful as aide mémoires, but to those who did not they often appear as a series of disparate papers with little co-ordination of subject matter and great variation in scientific content and literary style. This volume is unique in that it will delight its readers from cover to cover.

It is divided into three sections—physiology of photoreceptors, molecular biology and biochemistry of photoreceptors, and functional organisation of the retina. In each section significant advances have been made over the last few years, and these advances are related to a great extent by their discoverers. Few books of this type have contributions by such eminent authorities as Sir Alan Hodgkin, Professor H Gobind Khorana, and Professor John Dowling. Each of these are at the forefront of their field but still retain the capacity to relate the complexities of their work to the interested reader.

The section on physiology of photoreceptor cells is a model of clarity and with three contributions is a must for all students in the field of phototransduction. After reading these three papers it would be very difficult for any student to fail an examination on this subject.

The clarity of the text and the comprehensive nature of the contents are maintained in the section on molecular biology and biochemistry of the photoreceptors. Here the latest developments in the structure and function of rhodopsin are described together with the important recent

developments in terms of rhodopsin transport and the role of the interphotoreceptor matrix. This section finishes in the field of molecular biology with an extremely useful description of the role of genes in retinoblastoma.

The final section on functional organisation of the retina gives the reader an insight into the advances facilitated by the use of modern biochemical techniques and intracellular recording systems. Particular emphasis is given to the role of monoclonal antibodies in eliciting further information on transmitter systems in the neural retina.

This is a delightful book, beautifully written and well illustrated, and one that I would recommend to all my colleagues who have an interest in understanding the ways in which the retina works. I particularly recommend it to clinical ophthalmologists, for from one all too short volume they will be able to assimilate a quarter of a century of research. I congratulate the authors and now look forward to future volumes in this series.

JOHN MARSHALL

Spatial Vision. By RUSSELL L DE VALOIS AND KAREN K DE VALOIS. Pp. 381. £65.00. Oxford University Press: Oxford, 1988.

This monograph represents a summation of the experimental results and the views of this extremely distinguished team, and as such is welcome: it is a view of the visual world from Berkeley, and an interesting one at that. It will be used by those active in the field as a valuable source. The authors' presentation is heavily influenced by their belief that a form of piecewise harmonic analysis is carried out in the visual system. They adduce much evidence for this idea. For example, under certain circumstances cortical cells respond to the higher harmonics contained in a square wave grating as though they were carrying out a frequency analysis; the actual harmonic content is of course not perceived at all by the observer. For this reason Chapter 1 consists of a very clear and well illustrated introduction to linear systems analysis, pitched initially at so low a level that this reviewer anticipated that the book would consist of expanded lecture notes for students. However, parts of the book are extremely detailed, and there is no attempt to survey the field. Thus, although the first chapter ends with a warning, 'Quite different from applying Fourier analysis... is the construction of a machine to carry out Fourier analysis,' non-linearities are discussed only in the last chapter, no school of work which presents contrary views is mentioned, and the problem of how the brain defines both amplitude and phase is treated in a sanguine manner.

It is thus not clear for whom the monograph is designed. Its main concern is neurophysiology, and the applications to sensory psychology are very much secondary. It covers the entire visual system, dealing with optics, the anatomy of the visual pathway, retinal histology, photochemistry and visual transduction en passant. While each section would be required in a general textbook the emphases here are quite different. Thus the cortical magnification factor receives five pages (the authors have contributed to this problem by 2-deoxyglucose studies, and reproduce a handsome illustration), while the anatomy and histology of the primary, secondary, and tertiary cortical areas merit one page and no figure. Again, clinical measurement of low-frequency

contrast sensitivity is discussed, and in view of the authors' bias one might expect them to be enthusiastic. But: 'Many causes of high spatial frequency sensitivity loss are optical, and if so can often be alleviated by... spectacle lenses. Low spatial frequency losses in sensitivity cannot be corrected by such simple measures. Purely on practical grounds... it makes sense for clinicians to expend their limited time and resources on those problems which can be alleviated rather than others... which cannot be treated.'

Arguments such as that and omissions such as those noted above must detract from the book; moreover there are other problems. The section on transduction is out of date: there is no mention of the response shaping in peripheral retina, or the colour organisation of the primate visual system described last year by Hubel and Livingstone. Maybe the authors are not convinced by this work, but they should not dismiss it with a reference to 'Tootell *et al.* in preparation.' This is particularly unfortunate because their plate showing false colours is poor. It shows a red-yellow and a red-blue chequerboard, in which reds are meant to differ because of Bezold's effect. Although, as the caption states, the two sets of red squares *do* look different, this is due at least in part to very bad colour printing and not to any psychological or neurophysiological property of the viewer's visual system. Also, in general, the text refers to, but does not describe, the experiments and the results shown in the figures, and the captions are not in themselves long enough to provide instant understanding. This, combined with pages in which detailed arguments are highly compressed does not make for enjoyable reading.

G B ARDEN

The Vitreous and Vitreoretinal Interface. Eds CHARLES L SCHEPENS AND ADOLPHE NEETENS. Pp. 315. DM 128.00. Springer-Verlag: Berlin, 1987.

This book has been compiled by two of the more senior members on the international ophthalmic stage. There are 18 chapters, all dealing with different aspects of the vitreous. The book has been very well produced, and the overall effect is extremely pleasing. The chapter layout is clear, and the illustrations mainly of a very high standard, although it might have been nice to see more colour. (The legend for Fig. 2 on page 238 is inaccurate.)

As one would expect in a book devoted to a subject about a structure that is difficult to see and about which we are still extremely ignorant, the link between what is actually known and the clinical situations to which this knowledge is applied is rather tenuous. It is not therefore surprising that vitreoretinal surgeons would not agree with many of the clinical interpretations contained in this book. For example, it is surprising to see the use of intraocular gases under the title of 'vitreous substitution'. Again, the explanation of macular oedema in diabetes is contentious, as are the views expressed about open sky vitrectomy. One of the main clinical tools we have for studying the vitreous, particularly when there are opacities of the media, is ultrasonography. Many readers might have preferred a more thorough account of the diagnostic and prognostic value of this technique. Each chapter has been carefully referenced, with an extensive literature to allow further reading.

Anybody reading the book will come away with increased knowledge of this complex and challenging topic. I thoroughly enjoyed it and would recommend others involved in this work to read it.

A H CHIGNELL

Advances in Ophthalmic Plastic and Reconstructive Surgery. Vol. 6. **Orbital Trauma**, Part 1. Edited by STEPHEN L BOSNIAK. Pp. 419. No price given. Pergamon Press: New York. 1987.

Advances in Ophthalmic Plastic and Reconstructive Surgery. Vol. 7. **Orbital Trauma**, Part 2. Edited by Stephen L Bosniak. Pp. 351. No price given. Pergamon Press: New York. 1987.

These two volumes are the latest additions to the series 'Advances in Ophthalmic Plastic and Reconstructive Surgery'. 'Advances' is a misnomer, as the volumes contain reprints of classic historical monographs and dissertations on long-accepted techniques. However, the two volumes provide an extensive review of the topic with much of interest to the general ophthalmologist.

Both are multiauthor texts, and the reader is exposed to differing approaches to common problems such as blow-out fracture and the anophthalmic socket. The absence of unanimity highlights the fact that more advances are needed before ideal solutions are found.

The scope of the books is broad, with separate and often several chapters on traumatic optic neuropathy, fractures, traumatic ptosis, burns, and penetrating and gunshot wounds. Much of both volumes is devoted to fractures in the orbital region, with contributions from neurosurgeons, otolaryngologists, and plastic surgeons. These additions serve to inform the reader of techniques available to their patients and as such are valuable to the ophthalmologist. Each chapter has an extensive bibliography and each volume has a key word and author index.

A MCNAB

Atlas of Ophthalmic Surgery. Vol 2. **Cornea, Glaucoma, Lens**. Eds KLAUS HEILMANN AND DAVID PATON. Pp. 268. DM 270.00. Georg Thieme Verlag: Stuttgart. 1987.

The second volume of this atlas continues the same excellent pattern of combining superbly clear illustrations with a concise text; it has 18 internationally respected authors.

The first four sections cover anterior segment microsurgery of the cornea, chamber angle, ciliary body, lens, and trauma, with descriptions of 29 different procedures ranging from eight techniques in the management of cataract to more esoteric operations, including three types of block excision of the ciliary body. The final section describes the management of corneoscleral lacerations and anterior segment reconstruction.

The editors point out that it is not possible to include every surgical procedure. There is certainly a comprehen-

sive coverage of anterior segment procedures, but I think the account of keratorefractive surgical techniques should have been expanded beyond radial keratotomy, particularly to include the management of astigmatism. Modification of the techniques described would cover most other eventualities.

The particular value of this book is in allowing the reader to study in detail the techniques developed by surgeons highly skilled in these anterior segment procedures. The 561 step-by-step illustrations are accompanied by a short didactic text. The artwork is remarkable in its clarity, and there is never any confusion about the manoeuvres being demonstrated.

I would recommend this book to ophthalmic surgeons at all levels. The initiate would appreciate the clear step-by-step approach to the individual surgical procedures both to complement the early teaching and to clarify those operations not yet experienced. Many experienced surgeons studying this atlas may choose to modify their established technique in routine surgery and would like to refer to the book before performing the less common procedures.

R WILSON

Contemporary Issues in Ophthalmology: Refractive Keratoplasty. By IVAN R SCHWAB. Pp. 316. £45.00. Churchill Livingstone: Edinburgh. 1987.

While certain areas of refractive surgery have deservedly attracted a bad reputation, this burgeoning subspecialty has much to offer selected patients. This multiauthor volume is an excellent, up to date guide to the main techniques. Lamellar procedures such as epikeratophakia, keratomileusis, and plastic corneal inlays are covered as well as the incisional procedures such as radial keratotomy and relaxing incisions. Every chapter is easy to read, authoritative, and includes a comprehensive reference list. Inevitably some authors are rather too keen on their own techniques, but the average critical British ophthalmologist should have no problem in sorting the wheat from the chaff.

B L HALLIDAY

Immunopathologie de l'Oeil. By J P FAURE, E BLOCH-MICHEL, P LE HOANG, E VADOT. Pp. 430. 600F. Masson: Paris. 1988.

The authors of this book, which is in French, aim to cover all disorders affecting the eye which have an input from the immune system. In the introductory chapters they attempt to summarise current concepts in general immunology and specific knowledge of immune mechanisms in the eye. They describe in detail the immunopathology of a wide variety of ocular diseases, including infections, chronic inflammatory processes of all types, ocular tumours, and also corneal grafting.

In general, they achieve their aim, and the book will be useful for reference. An English edition would be necessary for readers whose French has not advanced beyond, at best, O-level standard.

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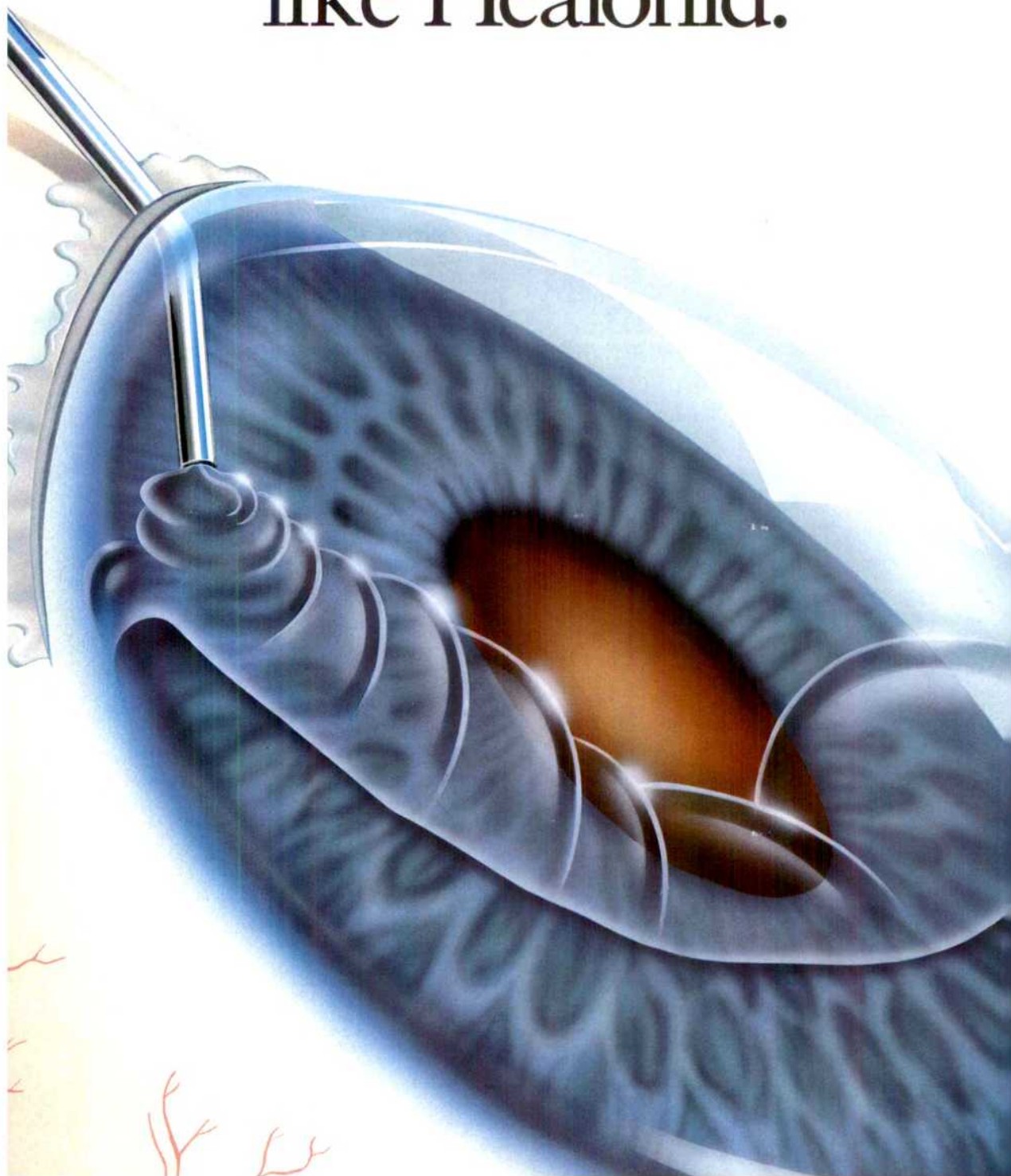
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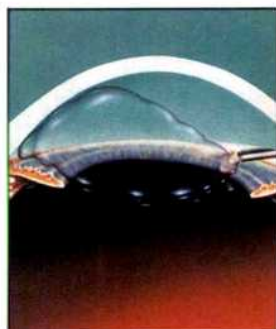
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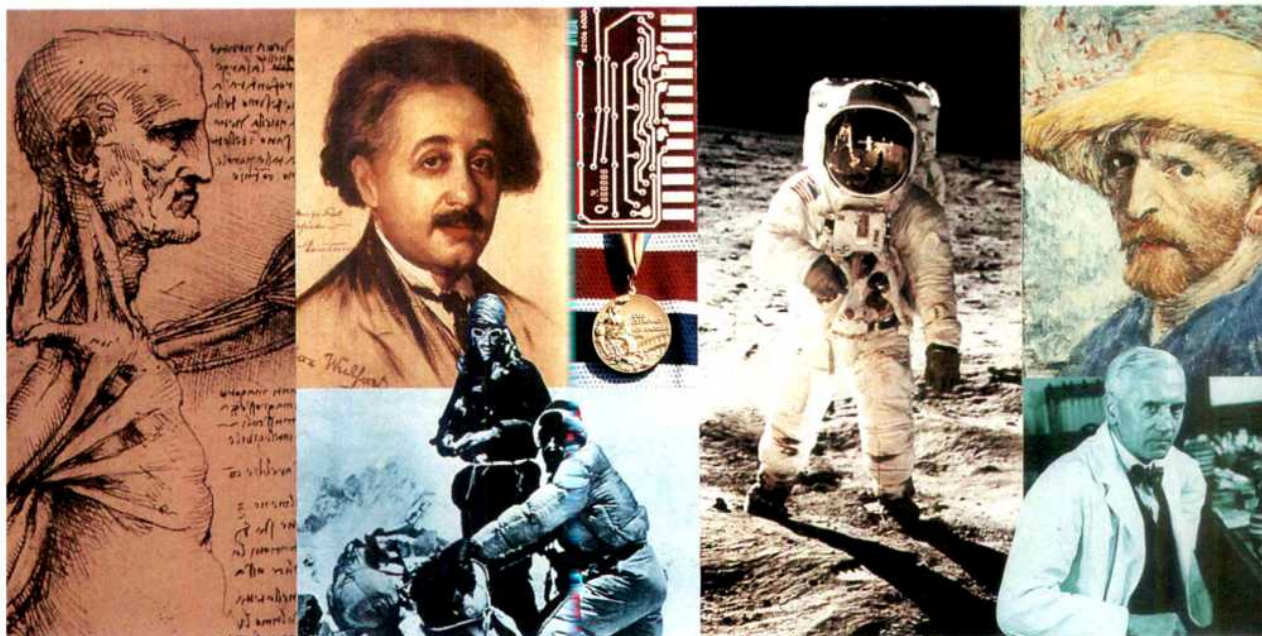
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Editorial: Monocular infantile cataract, intraocular lenses, and amblyopia

Those interested in amblyopia, unilateral cataract, and intraocular lenses in children should read the article by Burke *et al* in this issue. It raises again the problems that ophthalmologists face when trying to understand how to help these children.

The attainment of good vision in children after infancy with acquired unilateral cataract is no in question, but when the visual deprivation is from birth the prognosis is much worse, though there are several recent reports of good visual results.¹⁻⁴ To achieve these good results substantial obstacles have to be overcome: the patients have to be referred early, the surgery and optical correction should be completed successfully in the early days of the child's life, and amblyopia therapy should be started promptly and vigorously and continued for years. The critical problem in the management of unilateral congenital cataract is the amblyopia therapy.⁵ This necessitates adequate optical correction and occlusion of the healthy eye for several hours each day. If the treatment is completed later than six weeks of age, good visual acuity is rarely achieved, though there are reports of cases of truly congenital cataract in which acuities of 20/100 have been achieved with completion of treatment as late as 17 weeks of age. While a number of successful cases have been published, there must be many times that number of patients who have not achieved good acuity and have experienced considerable personal cost and inconvenience and some risk – for a condition which, if left untreated, is surely of minor significance to the child's life.

What represents a good visual result? Burke *et al* claim that 1/60 represents a significant improvement for a 'reserve eye'. Not all would agree with this, and vision compatible with a normal education (with some difficulty) might be more acceptable – say an acuity of 6/24. The age of surgery of Burke *et al*'s patients with non-traumatic cataract was 4.3 years and the youngest 0.3 years, so by current understanding they were unlikely to achieve good vision.

There are other than visual reasons for operating on unilateral cataract. They include the attainment of a good cosmetic appearance and the prevention of glaucoma from a swollen and anteriorly positioned lens in persistent hyperplastic primary vitreous. But for any possibility of good vision only treatment

completed by, at the latest, four months stands any chance of achieving good acuity – the earlier the better.

Units specialising in the optical correction of infant aphakia may expect to achieve over 80% acceptance rate of contact lenses in infancy.⁷⁻⁹ The ability to change the parameters of the optical correction is vital in view of the rapid changes in the eye in the first year of life. Spectacles can also be changed easily, but to treat adequately the amblyopia they have to correct up to 35 dioptres of hypermetropia, with attendant optical disadvantages.

Intraocular lenses have been implanted in children for many years.¹⁰⁻¹¹ The surgery is not without complications.¹² Binkhorst¹² found significant complications in his patients who were treated with IOLs and a number of complications have been outlined by Hiles.¹³ Some of these may be serious,¹⁴ especially with anterior-chamber or iris-supported lenses and those made of more than one material. With single-piece lenses the long-term complication rate may be less, but this has yet to be proved. Since the life expectancy of most children with cataract is normal, the lenses will have to last their three score years and ten. Successful short term follow-ups as in most published papers cannot throw light on these all-important risks. With careful techniques and the use of modern lens designs, materials, and positioning, the problems of implantation are not insurmountable, as Hiles¹³ and Burke *et al* show. It is whether IOLs provide a safe long-term optical correction that is by itself appropriate in the management of amblyopia that is under scrutiny.

Intraocular lenses or epikeratophakia alone cannot provide an adequate optical correction throughout infancy. With refractive errors changing from a retinoscopy of +35 dioptres to +18 in the first year, any lens adequate for early infancy is bound to be inadequate later in the first year, leaving the eye substantially myopic, and it is difficult to justify the implantation of an adult-power lens without additional optical overcorrection for at least the first years of life.

Unilateral traumatic cataracts and secondary intraocular lens implantation in older children after contact lens failure may provide some indications for the implantation of modern designs of lenses, but the

long-term uncertainties and the immutability of IOLs may still raise doubts in the minds of ophthalmologists with a longer-term view. Failure or likely failure of parents to co-operate with occlusion is not an indication, because it applies to them whatever the form of optical correction. Failure to use contact lenses is difficult to predict, and although, this may be an indication for alternatives to contact lenses, targetting the recipient is difficult. A more acceptable method might be to use continuous-wear contact lenses for the first year and to carry out epikeratophakia when the child is over 1 year old, with a spectacle overcorrection.

Papers such as that by Burke *et al* should be read with care and with considered reflection on the relevance of IOLs in the treatment of the real cause of the visual defect in early onset cataract – amblyopia. The ethical problems of implanting lenses in infants may perhaps be overcome if the parents can be made fully to understand the risks and difficulties of the various forms of treatment; if modern intraocular lens styles, materials, and surgery prove to be safe in the long-term; if they are tolerated as well as and have a complication rate as low as contact lenses; and if all efforts are directed to treating the amblyopia. This is quite a challenge and one not yet accepted or fulfilled.

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Editorial: Mollicutes: what are they?

An article in this issue (page 865) is concerned with the possibility that mollicutes are involved in the pathogenesis of so-called orbital pseudotumours. But what are mollicutes?

Delving into the literature reveals that they are a class of micro-organisms in the Prokaryote kingdom, that is, they are unicellular and, though they contain chromatin material, they do not have a distinct nucleus. There are two types or divisions of Prokaryote: Photobacteria, which are sensitive to light, and Scotobacteria, which are not. Of the Scotobacteria there are three classes: Bacteria, Rickettsia, and Mollicutes, the last being distinguished and defined by the absence of an outer cell wall. Hence the source of their name, from the Latin mollis, soft and cutis, skin. They are the smallest category of organism capable of growth in cell-free media.

Their existence has been known for some time although only in the last 10-15 years has their taxonomic position been clarified. Previously, mollicutes commonly went by the name of mycoplasmas, and it is still common practice for them to do so, but more recently it has become proper to reserve the term *Mycoplasma* for a defined genus within the Mollicute class. Many of the mycoplasmas and related genera are further distinguished by having a low proportion of guanosine plus cytosine in the base pairs of their cytoplasmic DNA and having a need of sterols, such as cholesterol, for growth.

In appearance those of relevance to the animal kingdom measure about 300 μm , are bounded by a single unit membrane but have no wall, are variably coccoid or filamentous in shape, and have a cytoplasm

composed for the most part of ribosomes and diffuse or filamentous chromatin.

What of their relevance to human pathology in general and to ophthalmology in particular? About a dozen different Mollicutes, mostly Mycoplasmas and related genera, have been identified in human tissues, most occurring as part of the normal flora coating the several mucosal surfaces and, as such, of little or no clinical consequence. Nevertheless, occasionally they may be associated with opportunistic infections of the mouth and urogenital tract. *Mycoplasma pneumoniae*, on the other hand, is an undoubted if weak pathogen in that it is a frequent cause of atypical pneumonia in young people. Another Mollicute of tick origin is cataractogenic when injected into suckling mice, but reports of ocular and adnexal disease due to mycoplasmas and related organisms are sparse, being restricted to accounts of conjunctivitis in the newborn and, with iridocyclitis, in Reiter's syndrome.

It is of some interest, therefore, that structures comparable to Mollicutes are now described in the cytoplasm of leucocytes present in biopsies from patients with inflammatory orbital disease, given that the aetiology of most so-called pseudotumours is at present quite obscure. The authors prefer the term mollicute-like organism, since the putative pathogen resists attempts at cultivation and is identifiable on ultrastructural criteria alone. Whether the entities described are indeed viable organisms involved in chronic orbital inflammation and, if so, whether they are causal or merely coincidental remains to be seen.

A GARNER

Intraocular lens implants for unocular cataracts in childhood

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SUMMARY We report the outcome of intraocular lens implantation in 20 children with visually significant cataracts (seven traumatic, 13 non-traumatic). Six patients had anterior and 14 had posterior chamber implants. The mean age of the whole group at the time of surgery was 5.9 years (range 0.3 to 15.1 years), while the mean period of follow-up was 2.4 years (range 0.8 to 5.9 years). Postoperatively 10 patients developed a transient fibrinous uveitis, four required lens repositioning, one needed lens removal, and eight required posterior capsulotomy. Complications warranting secondary surgical procedures occurred predominantly in eyes with posterior chamber implants. Co-operation with conventional amblyopia treatment was satisfactory in eight out of 16 patients. Postoperatively nine out of 18 patients had peripheral fusion, four patients regained visual acuities of better than 6/9, and visual acuity did not improve beyond 3/60 in six cases. In 19 eyes the optical pathway to the retina is clear and the implants are stable with no evidence of persisting inflammation. Contact lenses remain the initial treatment of choice in infancy, but modern intraocular lenses are well tolerated and have a role in the visual rehabilitation of patients with contact lens and probable contact lens failures and older children with unocular cataracts.

Before the early 1980s the child with a monocular congenital cataract was considered a virtually hopeless clinical problem, with successful visual rehabilitation practically unknown.^{1,4} But some recent studies show that such patients may benefit from early cataract extraction and intensive occlusion therapy initiated during the critical period for development of visual perception.⁵⁻⁸ While sometimes very rewarding, the successful management of these children is none the less difficult, time consuming, and requiring much compliance from the patient and motivation in the parents. A contact lens is the generally accepted treatment^{9,10} but is often given up or associated with complications.¹¹⁻¹³

In selected cases implantation of an intraocular lens (IOL) is an alternative, and encouraging results have been reported in patients with traumatic and monocular congenital cataracts.¹⁴⁻¹⁸ However, enthusiasm for this form of therapy has been tempered by initial discouraging results,¹⁹ complications specifically related to paediatric pseudo-

phakia,^{20,21} and the possibility of secondary complications many years after implantation. Recent advances in microsurgical techniques and intraocular lens design plus the availability of hyaluronidase and the neodymium (Nd) – YAG laser have reduced operative complications and facilitated their treatment.^{22,23}

We chose to implant posterior chamber and flexible one-piece anterior chamber lenses in a selected series of children with unilateral aphakia, believing that complications from an intraocular lens would be less significant than the inevitable severe amblyopia of inadequately treated cases.

Subjects and methods

We studied a consecutive series of 20 children who were treated with intraocular lenses following the removal of unocular cataracts. Seven had traumatic cataracts and 13 infantile cataracts of uncertain aetiology. Informed consent was obtained from the parents of each child in the study. The parents were given information on the risks, benefits, and alternatives to the procedure. Patients with non-traumatic

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cataract were selected for secondary lens implantation after failure with a contact lens or for primary intraocular lens implantation if the parent or child refused contact lens wear, or the ophthalmologist deemed that contact lens wear would not be successfully concluded owing to non-compliance of parent or patient, or owing to other social factors which precluded adequate contact lens follow-up and replacement. Patients with traumatic cataracts either had cataract surgery and IOL implantation in conjunction with reconstitution of the globe or as a second procedure when intraocular inflammation had settled.

Eighteen of our patients underwent lens aspiration with (4) or without (14) primary posterior capsulotomy. Fifteen of these had J-loop posterior chamber intraocular lenses (PC IOL) with prolene loops and three patients (cases 9, 15, 20) had flexible one-piece open loop polymethyl methacrylate (PMMA) anterior chamber lenses (AC IOL). Two patients after ocutome lensectomy (cases 2 and 8) also had secondary anterior chamber intraocular lenses implanted. Where possible in older children intraocular lens powers were calculated from keratometer readings, A-scan axial lengths, anterior chamber

depths, and refractive errors. A standard adult powered lens of between +19 dioptres and +21 dioptres was placed in children less than 3 years old, because of inaccuracies induced by growth of the eye.

Postoperatively, the patients were regularly examined by an ophthalmologist and orthoptist. Visual acuities before and after surgery were measured by the Stycar, Sheridan-Gardiner, or Snellen tests, and by acuity card procedure, or by observing ocular motor fixation patterns in patients too young to respond to subjective visual testing. When indicated, neodymium-YAG laser posterior capsulotomy was performed, generally with ease, in patients over 6 years old, while younger children usually required operative discussion under general anaesthesia.

Results

The mean age of the 20 children (Table 1) at the time of intraocular lens implantation was 5.9 years (range 0.3 to 15.1 years), while the mean age of the traumatic and non-traumatic groups was 8.8 and 4.4 years respectively. The level of pre- and postoperative acuities for both groups is shown in Table 2. Docu-

Table 1 Patient data

Patient no.	Age at IOL surgery (years)	Length of follow-up (years)	Aetiology of cataract	Type and power of implant	Surgical technique	Visual acuity		Post operative peripheral fusion	Compliance with occlusion	Refraction within 1.5 years of surgery
						Preop.	Current			
1*	12.7	1.4	T	PC 20D	Asp.	6/60	6/6	+		-0.75+1.0×15
2	3.4	3.6	T	AC 20D	OL‡	1/60	6/24	+	Fair	-1.50+3.0×120
3*	6.4	2.0	NT	(PC)† AC21D	Asp.	3/60	6/60	§	Poor	+3.0+0.5×160
4*	1.7	4.4	NT	PC 23D	Asp.	UCUSUM	3/60	§	Fair	-3.0+2.0×120
5*	1.4	5.7	NT	PC 21D	Asp.	UCUSUM	6/24	+	Good	-2.5+2.0×110
6*	4.7	2.2	NT	PC 19D	Asp.	UCUSUM	3/60	§	Fair	-1.50+0.25×160
7*	7.9	1.1	NT	PC 22D	Asp.	PL	2/60		Poor	+1.50
8	6.0	2.1	T	AC 22D	OL‡	6/36	2/60	+	Poor	+2.0+1.0×90
9*	5.2	1.3	NT	AC 21D	Asp.	2/60	6/36	+	Fair	+3.0+2.0×80
10*	15.1	1.1	T	PC 20D	Asp.	HM	6/9	+		-0.5+1.25×180
11*	0.3	5.9	NT	PC 21D	Asp. & C‡	UCUSUM	PL	§	Poor	IOL removed
12	12.1	1.2	NT	PC 19D	Asp.	6/36	6/9	+		+2.25+0.75×130
13	6.9	0.8	NT	PC 21D	Asp.	1/60	5/60	§	Fair	-3.50+2.0×150
14*	3.0	1.6	NT	PC 21D	Asp.	6/36	3/60		Poor	-1.50+1.75×80
15	4.5	2.3	T	AC 19D	Asp.	HM	2/60		Good	-1.50
16*	12.4	1.9	T	PC 21D	Asp.	1/60	6/18	+		-1.0+2.75×150
17	0.8	1.9	NT	PC 21D	Asp. & C	UCUSUM	PL	NA†	Poor	+7.50 contact lens
18	0.5	4.3	NT	PC 21D	Asp. & C	UCUSUM	2/60	§	Poor	-2.50
19	6.0	1.7	NT	PC 21D	Asp. & C	4/60	6/36	NA	Good	-0.75+1.00×165
20	7.7	1.6	T	AC 23D	Asp.	PL	6/4	+	Good	-1.75+1.25×95

T=traumatic, NT=non-traumatic, PC=posterior chamber IOL, AC=anterior chamber IOL, Asp.=lens aspiration, C=posterior capsulotomy, OL=ocutome lensectomy, PL=perception of light, HM=hand movements, UCUSUM=uncentral, unsteady, unmaintained fixation, considered equivalent to <1.5/60, NA=not available, Patient 11=microphthalmos and nystagmus, Patient 18=microphthalmos and congenital syphilis, +=present.

*Patients who require secondary surgical procedures. †PC IOL replaced by AC IOL, ‡Contact lens failure, §Strabismus.

mented preoperative heterotropia was present in six cases; two eyes were microphthalmic (cases 11 and 18), but no patient had nystagmus. One child (case 2) had an oculectomy, contact lens, and penetrating keratoplasty at the age of 2 years after a penetrating corneal injury.

The most frequent early postoperative complications was a fibrinous uveitis, which usually began after 24 hours and required topical corticosteroids (Table 3). One patient (case 8) had a small hyphaema, and one had transient superior half corneal oedema (case 6). During the mean follow-up period of 2.4 years (AC IOL 2.1 years, PC IOL 2.5 years) the majority of complications occurred in cases with posterior chamber intraocular lens implants (Table 3). These were iris implant synechiae and visually significant posterior capsular opacification. Eight patients (Table 4) required surgical or Nd-YAG laser capsulotomies, one of whom (case 18) had already had a primary capsulotomy. Five cases had the PC IOL haptic dislocated and held forward in the iris-pupil plane by synechiae. Three of these had an uneventful repositioning of the PC IOL haptic with no recurrence, and one patient (case 3) had the PC IOL replaced without difficulty by an AC IOL with no subsequent complications. One patient (case 11) had the PC IOL removed and replaced by a contact lens.

None of our patients had cystoid macular oedema clinically, though fluorescein angiography was not performed. Retinoscopy after operation showed low degrees of hypermetropia or myopia in most cases (Table 1). One patient (case 17) had a significant anisometropia requiring a +7.5 dioptre overcorrection with a contact lens at six months. There was only one case of postoperative astigmatism greater than 2.75 dioptres, and this occurred in a patient (case 2) who had a previous corneal graft. Sixteen patients were on intensive occlusion therapy postoperatively (up to seven hours per day) with variable compliance and visual rehabilitation (Table 1). It was possible to test fusion potential in 18 patients by means of a synoptophore, nine of whom showed variable degrees of peripheral fusion.

Discussion

The visual results following removal of monocular cataracts from infants' eyes are often disappointing. Though the prognosis for attainment of good acuity and fusion in older children is poorer, surgery should be considered in selected cases, as it may be impossible to date the onset of cataract and visual deterioration with any degree of precision.²⁴ Untreated until adult life these patients may have acuities of perception of light only.²⁵ Even an acuity of 1/60 represents a

significant improvement on this for a reserve eye. Only two patients in this series have a current acuity poorer than 1/60.

Contact lenses, the standard optical treatment, are associated with many problems. These include infections, sterile inflammations,²⁶ and induction of morphological changes in the epithelium²⁷ and endothelium.²⁸ In addition, many parents are unable to cope with the care of their children's long-term contact lens, which can be a source of considerable stress to both the child and family.

Epikeratophakia is an alternative option in cases unsuitable for contact lens wear. One problem of this procedure has been the slow return of visual function to preoperative levels owing to gradual clearing of the tissue lens in patients who are already amblyopic. Recent studies^{29,30} have yielded encouraging results in patients less than 18 years old.

Table 2 Present and preoperative acuities of patients with traumatic and non-traumatic unocular cataracts

Visual acuity	Number of cases with each type of cataract			
	Traumatic (7)		Non-traumatic (13)	
	Visual acuity		Visual acuity	
	Preoperative	Current	Preoperative	Current
≤6/9	—	3	—	1
6/12–6/36	1	2	2	3
6/60–3/60	1	—	2	5
2/60–1/60	2	2	—	2
<1/60	3	—	9	2

Table 3 Postoperative intraocular lens complications

Complications	Anterior chamber implants (5 cases)	Posterior chamber implants (15 cases)
Fibrinous uveitis	3	7
Visually significant posterior capsule opacities	—	6
Iris – implant synechiae	—	9
Iris sphincter erosion	—	2

Table 4 Secondary surgical procedures

Procedure	Anterior chamber lens (5 cases)	Posterior chamber lens (15 cases)
Posterior capsulotomy (surgical/Nd-YAG)	—	8
IOL repositioning	—	3
IOL replacement	—	1*
IOL removal and pupilotomy	—	1

*Posterior chamber implant replaced by an anterior chamber implant.

So far, however, no controlled trial in children comparing epikeratophakia with intraocular lens implantation has been carried out.

In adults intraocular lens implantation is superior to contact lenses in achieving good binocular function.³¹ However, ophthalmologists continue to disagree about lens implantation in children. Some stress their usefulness, other consider them impracticable. Hiles has shown that non-compliance by the patient in accepting the best optical correction is lower in those who have an intraocular lens than in those with a contact lens, though compliance in accepting occlusion for amblyopia remains an equal problem in both groups.³²

The effect of intraocular lenses on the growth, development, and structures of the child's eye remains speculative, but a recent study³² described their short-term safety and predictability, finding no histopathological evidence that the child's eye tolerated an intraocular lens less well than an adult's. Our 20 cases represent a heterogeneous group of traumatic and non-traumatic unioocular cataracts. The visual results were encouraging in that nine of 18 patients assessed had peripheral fusion, four had final acuities of better than or equal to 6/9, while the acuity of six patients measured <3/60. Intraocular lenses were generally well tolerated and anatomically stable in 19 eyes, with no evidence of persisting inflammation.

We found that the prevalence of postoperative complications, particularly visually significant posterior capsular opacification and early postoperative lens malposition (Table 3), to be higher in children with posterior chamber implants. By contrast, a smaller group who had flexible anterior chamber implants were relatively free of pupil complications irrespective of the presence or absence of the posterior capsule. Hiles and Hered report a similar trend in a larger group of patients.³³ They found that secondary membranes and lens malposition occurred in 22% and 7% respectively of eyes with anterior chamber implants compared with 63% and 40% in eyes with posterior chamber implants. They also note that secondary membranes developed earlier in eyes with posterior chamber implants.

Like others we evaluate the best optical correction in the context of the dynamic growth of the eye and the changes in refractive power that occur throughout childhood. In our experience the preferred treatment for the infant with compliant parents is lensectomy or lens aspiration plus capsulotomy, contact lens wear, and intensive occlusion therapy. There are nevertheless patients within this group who fail to achieve adequate contact lens wear, with many episodes of interrupted treatment and a poor visual outcome. We consider that they form a particular indication for secondary anterior chamber lens implantation in the

hope of at least retaining useful peripheral vision. One of our patients (case 2) who was intolerant of a contact lens remained binocular with useful vision following intraocular lens implantation. Likewise, patients with unioocular traumatic or late-onset developmental cataracts, who may have already developed binocularity, could be considered for intraocular lens implantation (Table 2), as high power aphakic contact lenses may induce sufficient aniseikonia (approximately 16%) to prevent achievement of optimal binocularity.³³

Intraocular lenses as a first step or in cases of contact lens intolerance have a role in the treatment of the paediatric aphake. It has been our experience that children generally tolerate intraocular lenses well and that flexible anterior chamber implants are associated with fewer short term complications than posterior chamber intraocular lenses (mean follow up 2-4 years). In 19 of the 20 children the implants are stable, the eyes quiet, and the optical pathway to the retina clear. The visual outcome in non-traumatic cataracts depended chiefly on the severity of amblyopia at the time of surgery and compliance with postoperative occlusion therapy.

While contact lenses remain the initial treatment of choice in unioocular cataracts in infancy, intraocular lenses are well tolerated and have a role in the treatment of contact lens failures and older children. Flexible anterior chamber lenses may be preferred to posterior chamber implants for the treatment of children under 6 years old in view of their superior performance in this and other series.

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Accepted for publication 24 April 1989.

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twice daily for bacterial conjunctivitis

▼ Prescribing Information.

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Mills, K.B. et al. British Journal of Clinical Practice, 1987; Supplement 50: **41**: No.6, 10-12.

Scoville, B. et al. American Journal of Ophthalmology, 1988; **105**: No.2, 150-154.

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Negishi, C. Acta Soc. Ophthalmol. Jpn., 1982; **85**: 57-66.

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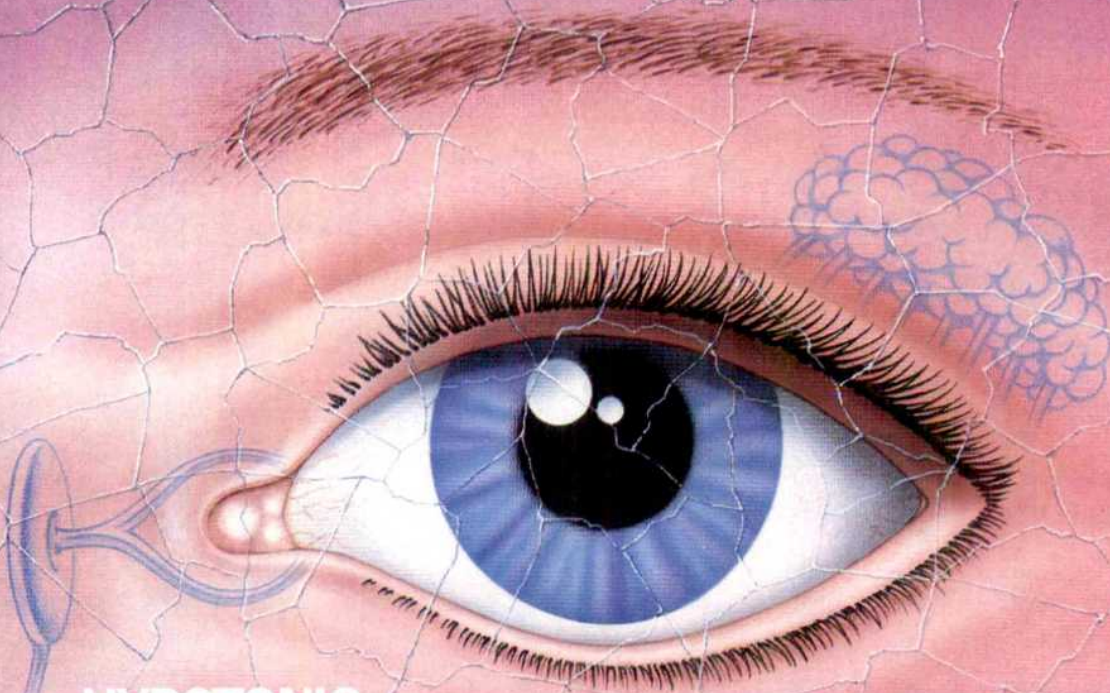
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ALLERGAN PHARMACEUTICALS

SCIENCE WITH VISION

Chronic orbital inflammatory disease: parasitisation of orbital leucocytes by mollicute-like organisms

EMIL WIROSTKO,¹ LEWIS JOHNSON,² AND BARBARA WIROSTKO¹

From the ¹Edward S Harkness Eye Institute and the ²Department of Pathology, Columbia-Presbyterian Medical Center, New York, and the ³College of Physicians and Surgeons, Columbia University, New York, USA

SUMMARY Chronic orbital inflammatory disease (COID) is usually considered non-infectious and idiopathic. Treatment is empirical, palliative, and may not prevent disease progression. COID occurs in isolation or in association with various systemic diseases. Exophthalmos may be an important presenting sign. Vasculitis, lymphoid infiltrates, and granulomas are common. Mollicute-like organisms (MLO) parasitising and destroying vitreous leucocytes are often found to cause human chronic uveitis when an appropriate search is made. Inoculation of these MLO into mouse eyelids produced chronic uveitis and exophthalmic orbital inflammatory disease. Mollicutes are cell wall deficient bacteria. Extracellular mollicutes cause human and animal diseases characterised by lymphoid infiltrates, immunosuppression, and autoantibody production. Intracellular morphologically similar bacteria are non-cultivable pathogens termed MLO. Identification is based on direct detection in diseased cells by transmission electron microscopy. MLO are cytopathogenic and detection is aided by the alterations they produce. MLO replace the cytoplasm, destroy the organelles, and alter the nucleus. This results in cell proliferation, destruction, and dysfunction. MLO parasitise lymphocytes, monocytes, and polymorphonuclear leucocytes. This report describes orbital leucocytes parasitised by MLO in three patients with isolated COID. Rifampicin treatment of MLO disease is discussed.

Chronic orbital inflammatory disease (COID) is usually considered to be non-infectious and idiopathic.¹ It occurs in isolation or in association with various systemic diseases.¹ Exophthalmos may be an important presenting sign.¹ Vasculitis, lymphoid infiltrates, and granuloma formation are common pathological features.¹ Mollicute-like organisms (MLO) parasitising and destroying vitreous leucocytes are often found to cause chronic uveitis in patients when an appropriate search is made.²⁻⁶ Inoculation of these MLO into mouse eyelids produced chronic uveitis⁷ and exophthalmic orbital inflammatory disease.⁸ MLO became disseminated to produce lethal chronic inflammatory disease in all organs.⁷⁻¹⁰ MLO-parasitised leucocytes were detected in all the diseased organs.⁷⁻¹⁰ The disease was progressive and similar in all the organs.⁷⁻¹⁰ The initial lesion was a vasculitis.⁷⁻¹⁰ This led to tissue lysis, lymphoid infiltrates, and granuloma formation.⁷⁻¹⁰

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Mollicutes are cell-wall-deficient bacteria.¹¹ They can be overlooked or confused with viruses.¹²⁻¹³ Their ultrastructural appearance¹⁴ is characteristic. Extracellular mollicutes are fastidious,¹⁵ lipid-rich,¹⁶ and contain a variety of potent cytotoxic substances including nucleases.¹⁷ Extracellular mollicutes cause human and animal diseases characterised by lymphoid infiltrates, immunosuppression, and autoantibody production.¹⁷⁻²⁰

Some morphologically similar organisms are intracellular pathogens.^{2-6, 17, 21-24} Despite considerable efforts at cultivation by many investigators the consensus is that these mollicute forms are non-cultivable.^{2-6, 17, 21, 22} Their taxonomy is uncertain and they are termed MLO.¹³ Identification of MLO is based on direct detection within parasitised cells by transmission electron microscopy.^{2-6, 17, 21-24} MLO are cytopathogenic and their detection is aided by the ultrastructural alterations they produce. They replace the cytoplasm and destroy the organelles,^{2-6, 21, 25} and they also alter the nucleus, probably as a result of nuclear parasitisation^{2-6, 25} and release of nuclease.²⁴

This results in cell proliferation, destruction, and dysfunction.¹³ A common and important feature of MLO disease is vascular involvement.^{1,2,10,13,21}

MLO parasitise lymphocytes,⁴ monocytes,⁵ and polymorphonuclear leucocytes.³ They appear as undulating filaments of 0.005–0.01 μm diameter, and pleomorphic trilaminar membrane-bound 0.01–1.0 μm tubulospherical bodies. Some forms develop into spore-like 0.5–0.7 μm cocci by deposition of electron dense material within the trilaminar membrane.³ The cocci have distinctive ultrastructural features.^{2,3} The following report describes the results of a search for MLO parasitised leucocytes in the orbital tissues of patients with isolated COID.

Materials and methods

Three patients with COID served as sources of the study materials. None had a history of thyroid, bowel, or other systemic disease. On physical examination all had normal signs and no evidence of peripheral lymphadenopathy. The results of routine studies of urine, blood cells and chemistry, and thyroid function were within normal limits in all three, and the chest roentgenogram of each was normal. The COID of each patient was considered to be non-infectious.¹ Microbiological studies were not conducted on the excised orbital tissues.

Patient 1 was a 17-year-old female with a two-year history of progressive left upper eyelid ptosis. Orbital computed axial tomograms were normal. Two

separate attempts at surgical correction were initially successful, but there was gradual return of the ptosis. During a third corrective procedure abnormal orbital tissue was noted and excised.

Patient 2 was a 61-year-old female with a six-year history of progressive exophthalmos limited to the right orbit. Computed axial tomograms performed at the onset of the disease showed right orbital patchy non-confluent radiodensities and normal extraocular muscles. The left orbit was normal. Biopsy then showed chronic non-specific inflammation. Treatment at that time consisted of combination radiation and chemotherapy. This arrested the disease, but five years later progressive exophthalmos recurred. A repeated computed axial tomography displayed progression of the right orbital disease. The contralateral orbit was again normal. A biopsy of the diseased tissue was taken, and that material was studied in this report.

Patient 3 was a 65-year-old female with a five-month history of progressive exophthalmos of the right orbit. Computed axial tomograms showed patchy right orbital non-confluent radiodensities and normal extraocular muscles. The contralateral orbit was normal. An orbital biopsy was performed.

A portion of each patient's specimen was fixed in 10% formalin, processed for routine paraffin-embedded histological sections, and stained with haematoxylin-eosin. Another portion of each patient's specimen was finely minced, fixed in 150 mM cacodylate buffered 2% glutaraldehyde, post-

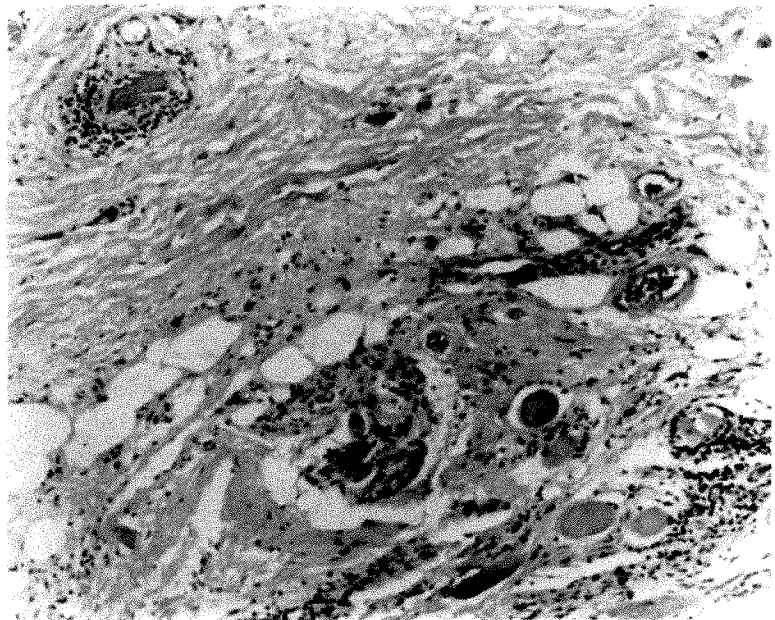


Fig. 1 Case 1. Chronic vasculitis involving arterioles, capillaries, and adventitia of small arteries. (Haematoxylin-eosin, $\times 110$).

fixed in osmium tetroxide, and embedded in Araldite (R). All these materials were available for investigational purposes through an Institutional Review Board exempt protocol. The sections stained with haematoxylin-eosin were studied for COID diagnostic concurrence under a light microscope. Thick sections embedded in Araldite (R) and stained with toluidine blue were also studied for leucocyte-rich foci under a light microscope. Multiple ultrathin sections were prepared from such foci and stained with uranyl acetate-lead citrate. All available leucocytes in these sections were studied for leucocyte alterations and MLO parasitisation by a transmission electron microscope.

Results

HISTOLOGICAL STUDIES

The numbers of leucocytes varied on each patient's specimen (Figs. 1–3). Lymphocytes were the predominant leucocyte in each specimen, but a few scattered monocytes and polymorphonuclear leucocytes were also present. Vasculitis was detected in each specimen, but it was most evident in the specimen from patient 1 (Fig. 1). Each specimen also showed scattered minute lytic foci in the extravascular adipose tissue. The specimen from patient 2 showed an intense diffuse lymphoid infiltrate (Fig. 2). The specimen from patient 3 showed several non-necrotic, non-confluent, epithelioid granulomas interspersed between focally intense lymphoid infiltrates (Fig. 3). Ziehl-Nielsen, Gomori's metha-

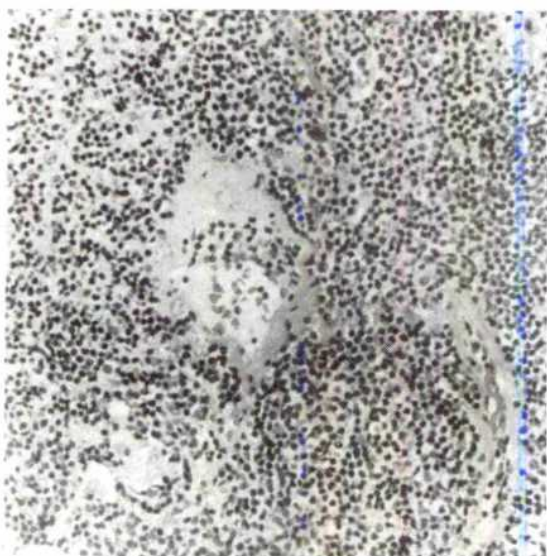


Fig. 2 Case 2. A diffuse lymphocytic infiltrate; an inflamed arteriole is also detectable. (Haematoxylin-eosin, $\times 155$).

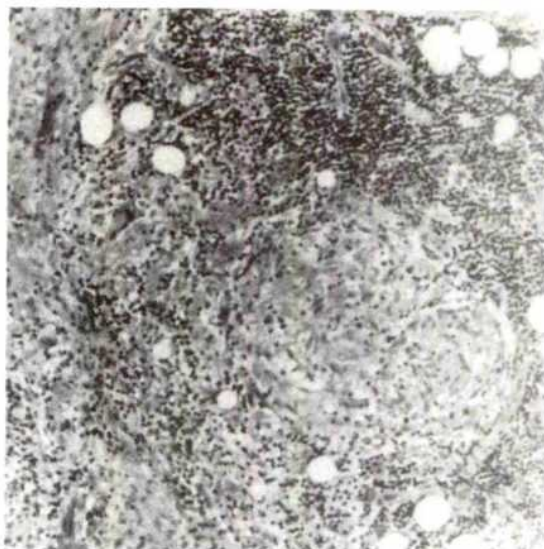


Fig. 3 Case 3. Non-necrotic epithelioid granuloma, a lymphocytic infiltrate, and fibrosis. No acid fast bacilli or fungi were detected in this specimen. (Haematoxylin-eosin, $\times 100$).

namine silver, and periodic acid Schiff stains on this specimen were negative for acid fast bacilli and fungi.

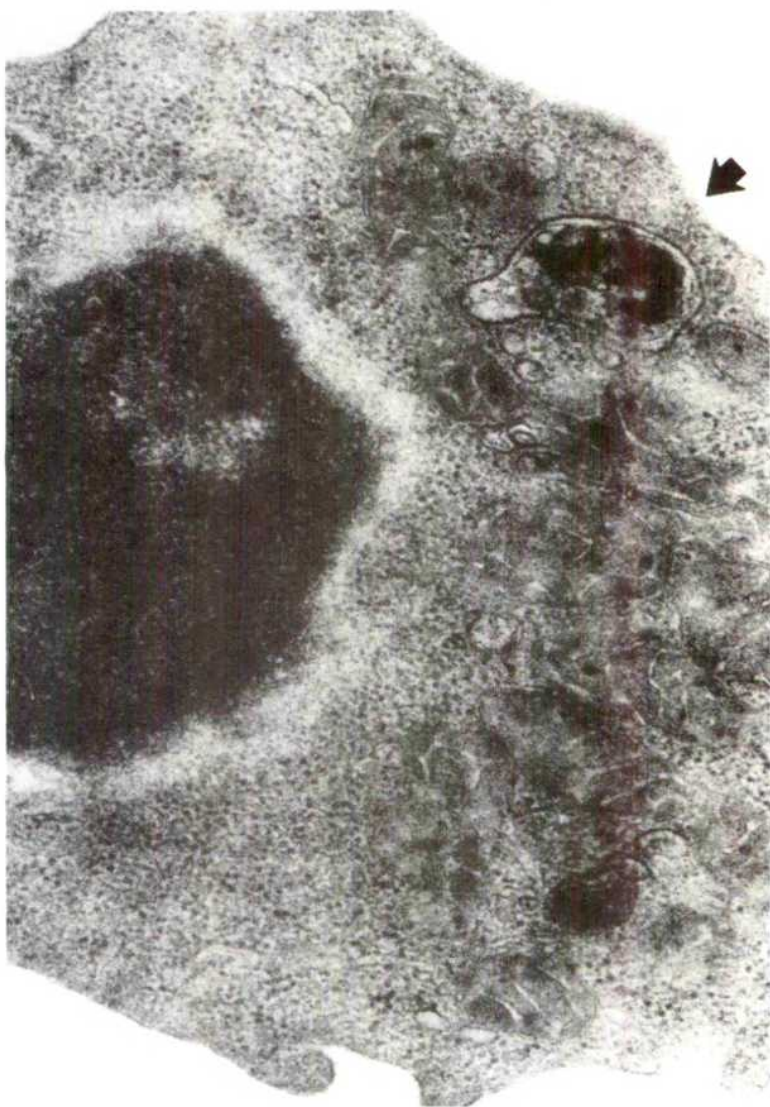
TRANSMISSION ELECTRON MICROSCOPIC STUDIES

About 2–10% of all the leucocytes in each patient's specimen displayed intracytoplasmic undulating filaments, 0.005–0.01 μm diameter, and pleomorphic trilaminar membrane-bound 0.01–1.0 μm tubulo-spherical bodies (Figs. 4,5). Some of these bodies exhibited deposition of intramembranous electron dense material to form 0.5–0.7 μm cocci (Fig. 5). All these cocci had thick cell walls, a distinct periplasm, and complex internal tubulofilamentous substructures. Nuclei of leucocytes harbouring the abnormal bodies often had ragged, irregular contours, chromatin clumping with lysis, and prominent perinuclear electron lucency (Figs. 4,5). In the polymorphonuclear leucocytes these bodies were usually associated with cytoskeletal lysis and a paucity of normal granules (Fig. 5).

Discussion

This study shows the diagnostic value of examining leucocyte COID lesions by transmission electron microscopy. Clinically and pathologically each patient's disease was considered to be non-infectious and idiopathic.¹ However, the leucocytes in each specimen contained intracytoplasmic bacteria-like bodies. Most of these lacked a cell wall. Some

Fig. 4 An aggregate of undulating tubules replaces the cytoplasm on the right. The remaining cytoplasm appears normal. A prominent flask shaped body (arrow) with a distinctive limiting membrane and complex internal substructures is also apparent. The nucleus shows diffusely dense chromatin, a markedly irregular contour, and a prominent perinuclear electron-lucent halo. (Uranyl acetate-lead citrate, $\times 53\,300$).



of these forms elaborated distinctive spore-like cocci. The organisms were morphologically indistinguishable from the MLO that produced chronic orbital inflammatory disease in mice.^{2,4} they produced nuclear and cytoplasmic alterations similar to those caused by the other MLO.^{2,5} They parasitised a similar wide range of leucocyte cell lines.^{2,5} We believe that these bacteria were MLO and caused the COID in these patients.

Study of polymorphonuclear leucocytes facilitates MLO detection. As in other chronic inflammatory diseases,²⁵ polymorphonuclear leucocytes are present in MLO diseases.^{3,6} Prominent cytoplasmic lysis

occurs in these leucocytes as a result of MLO parasitisation.^{3,6} The smallest MLO particles, namely, the 0.005–0.01 μm diameter filaments, are readily detected in the lysed cytoplasm.^{3,6} Furthermore, cell wall material forming distinctive spore-like cocci is often deposited in these cells.^{2,3,6} The lipid rich polymorphonuclear leucocyte cytoplasm²⁶ may enhance MLO growth and development.¹⁵

Chronicity was a noteworthy clinical feature of the MLO orbital disease in all three patients. Progression to exophthalmos occurred in two of them. All had chronic inflammation with various features including vasculitis, tissue lysis, lymphoid infiltrates, and

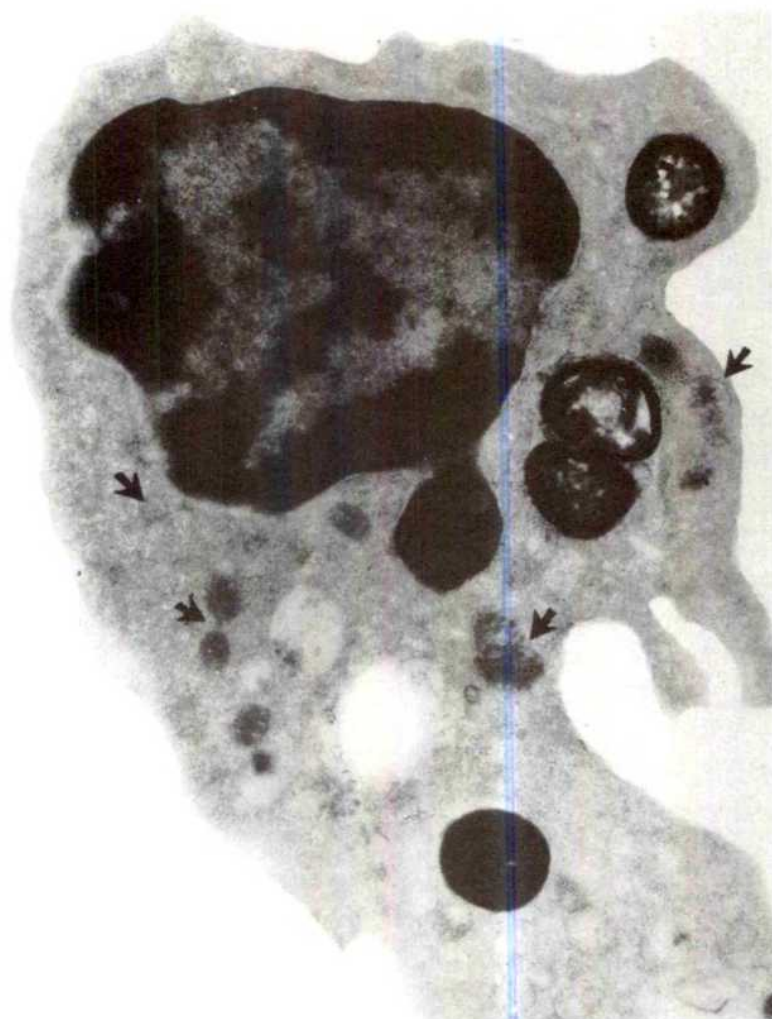


Fig. 5 Several spore-like cocci are apparent. Undulating pleomorphic tubulospherical bodies (arrows), some with internal structures, are also detectable. The cytoplasm shows patchy lysis and a paucity of normal granules. The nucleus displays several electron lucent chromatin foci of 'moth eaten' appearance, a ragged irregular contour, and a perinuclear electron lucent halo. (Uranyl acetate-lead citrate, $\times 20\,900$).

granuloma formation. In the mouse orbit MLO inoculation produced similar chronic inflammation.⁸ The mouse disease was progressive, leading to exophthalmos, and vasculitis of small vessels was the initial lesion.⁸ The mouse MLO orbital inflammatory process resulted in tissue lysis, lymphoid infiltrates, and granuloma formation.⁸ Disease chronicity and progression in the mouse was attributed to MLO disruption of the host inflammatory process.^{8, 10}

MLO were found in all three patients studied. A search for MLO as a cause of COID in other healthy patients needs to be conducted to expand these observations. Moreover, the results of MLO experimental mouse disease suggest that MLO may be a cause of human idiopathic systemic inflammatory diseases in addition to orbital disease.^{2, 9, 10} COID

frequently occurs in association with chronic bowel, thyroid, and joint diseases.¹ COID patients with such associated systemic diseases need to be investigated for MLO. The search should be conducted on both the orbital and systemic disease.

MLO diseases respond to long-term administration of appropriate antibiotics.^{27, 28} Rifampicin was tried in the treatment of MLO experimental mouse disease and it significantly decreased the morbidity and mortality in comparison with untreated infected controls.²⁸ Rifampicin was subsequently used to treat human MLO uveitis unresponsive to corticosteroids in uncontrolled studies.²⁸ With prolonged rifampicin administration the ocular inflammation subsided, allowing reduction or discontinuation of corticosteroid.²⁸ Rifampicin is a broad spectrum intra-

cellularly acting inhibitor of bacterial DNA-dependent RNA polymerase and is safe for prolonged administration.²⁰ It seems to be indicated in the treatment of orbital disease where MLO are demonstrated. Empirical administration of rifampicin may be considered in COID patients where MLO cannot be excluded by transmission electron microscopy of tissue leucocytes and the disease is progressive.

The authors are grateful to the physicians and technical staff of the Edward S Harkness Eye Institute, Columbia-Presbyterian Medical Center, New York, NY, whose co-operation enabled them to conduct this investigation.

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The recommended dosage is one drop instilled into the affected eye twice daily. Newly diagnosed patients should be treated in the first instance with Glauline 0.1%, changing to a higher strength if adequate control is not achieved or maintained. Patients on existing therapy, whether or not this is to be continued, should receive 0.3% Glauline and the intraocular pressure of all patients should be monitored regularly (e.g. every 4-6 weeks).

Use of the 0.6% strength is only recommended in patients who are not controlled on the lower strengths of Glauline.

CONTRA-INDICATIONS, WARNINGS ETC.

The use of Glauline is not recommended in patients with obstructive airway disease, cardiac failure or hypersensitivity to metipranolol. Beta blockers should not be given with verapamil and neither drug should be administered within several days of discontinuing the other. As absorption into the circulation is possible, Glauline should only be used

with caution in patients already receiving similar drugs by mouth. In particular, care should be taken in patients with sinus bradycardia and greater than first degree heart block. Although there is no evidence to suggest that metipranolol has teratogenic properties, its use during pregnancy should be avoided, unless the potential benefits are considered to outweigh the possible hazards. No clinical trials in children have been carried out. Glauline should not be used in patients fitted with soft (hydrophilic) contact lenses.

PHARMACEUTICAL PRECAUTIONS

Glauline should not be diluted or dispensed from any container other than the original bottle. It is potent for three years unopened, but as with other eye drops the contents of each bottle should be discarded one month after opening.

LEGAL CATEGORY - POM

PACKAGE QUANTITIES

Glauline is supplied as a sterile ophthalmic solution in a 5ml plastic dropper bottle.

FURTHER INFORMATION

Glauline has little or no effect on pupil size or accommodation. Glauline is generally well tolerated but some patients may complain of a slight stinging which soon passes off. Transient headaches have also been reported.

PRODUCT LICENCE NUMBERS

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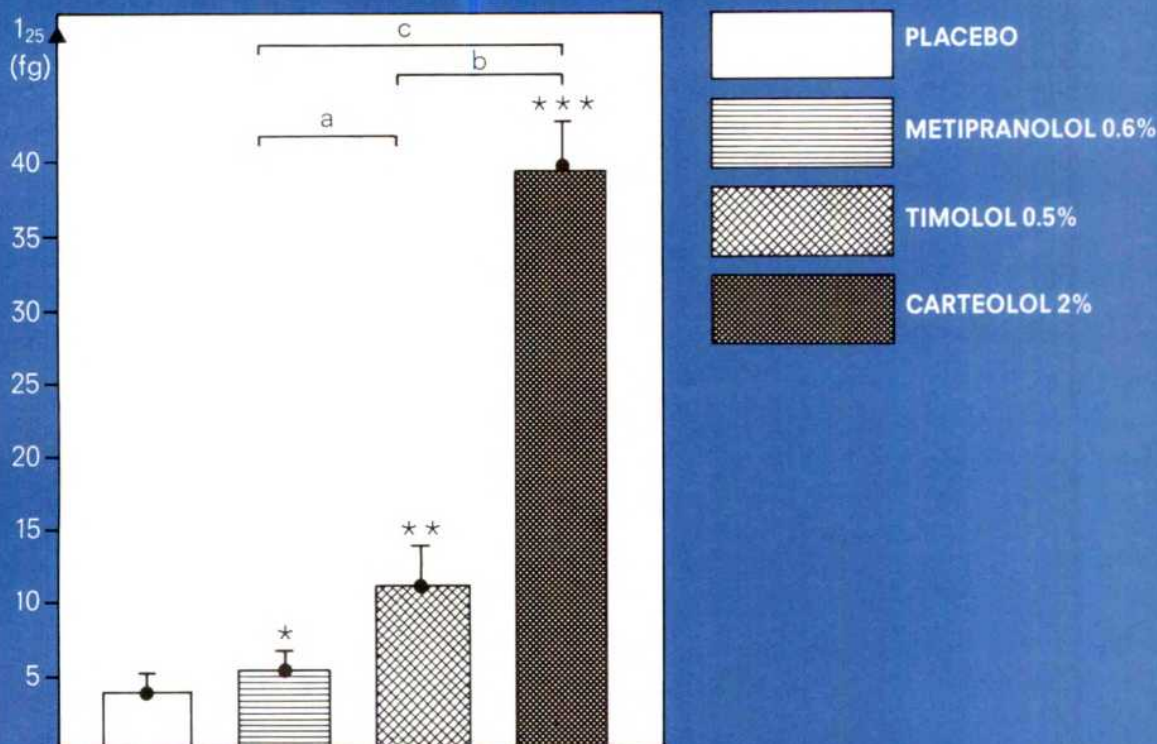
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(a) Isoprenaline challenge test¹



Dose of isoproterenol hydrochloride (mean $\pm$ SE) required to increase resting heart rate by 25 bpm (I_{25}) 3 hours after one drop of ophthalmic β -blocker in each eye. (* $P < 0.05$; ** $P < 0.001$; *** $P < 0.0005$ vs. placebo; a, $P < 0.02$; b, $P < 0.001$; c, $P < 0.001$.)

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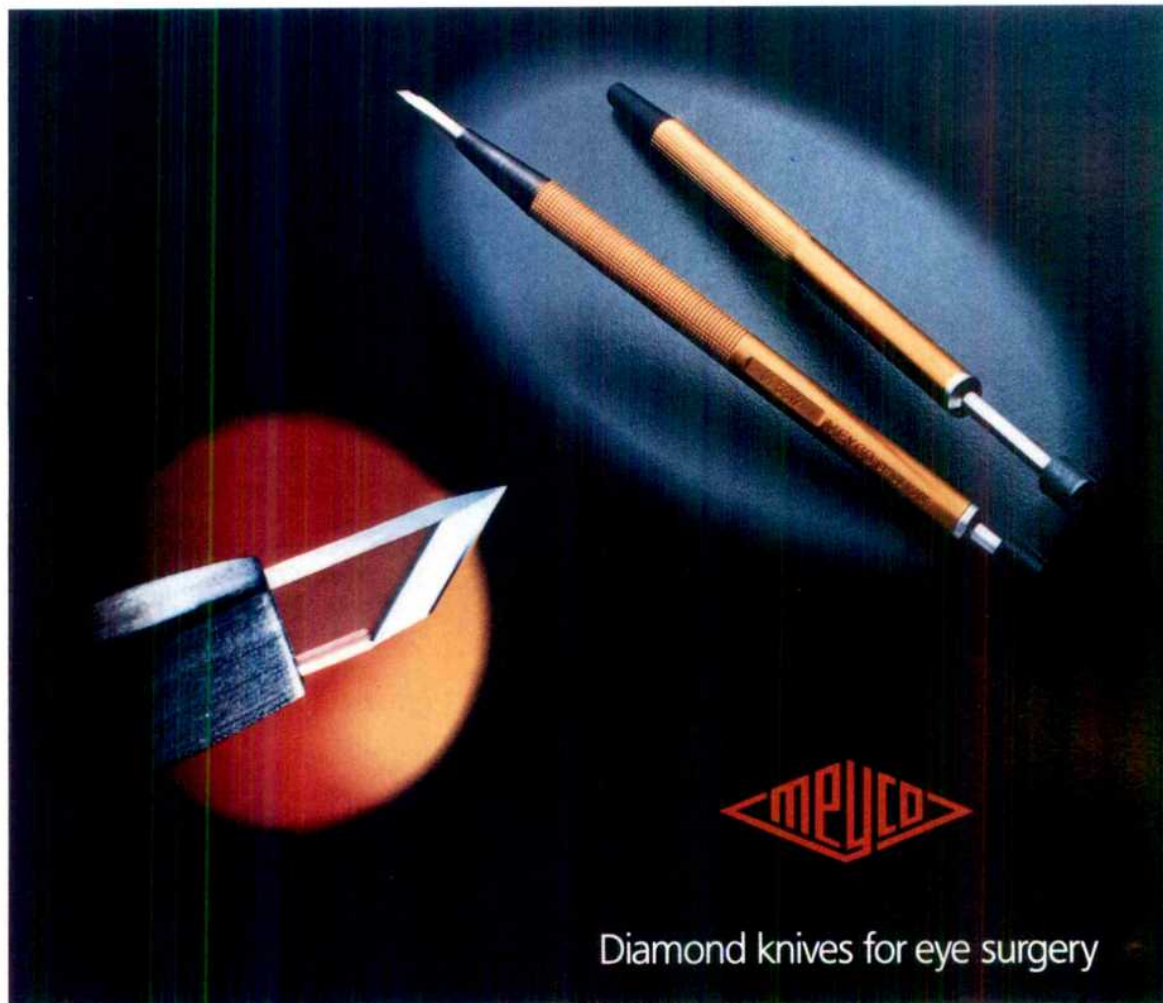
(b) Exercise Tachycardia²

"Timolol significantly reduced exercise tachycardia ($P < 0.05$) an effect which was not shown by metipranolol 0.1% or 0.3%."

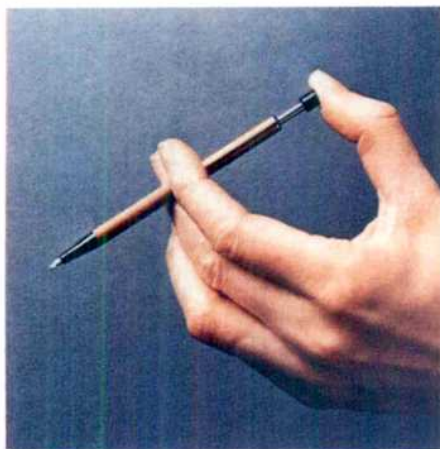
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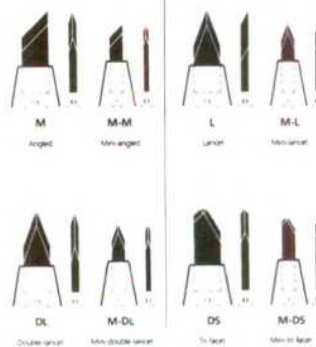
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Human fetal iridocorneal angle: a light and scanning electron microscopic study

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SUMMARY The iridocorneal angle and inner layers of the trabecular meshwork in human fetal eyes were studied by scanning electron microscopy. Tissue from 32 eyes of 17 fetuses with a gestational age from 12 to 22 weeks were investigated in order to determine the morphological changes in the cellular lining of the anterior chamber angle recess during development. The findings indicate that, although hexagonal corneal endothelial profiles extend almost to the angle apex in a few of the younger eyes examined (12–14 weeks), the lining is always perforated by a few discrete intercellular gaps (2–6 μm diameter). As development progresses it becomes clearer that the maturing meshwork is lined by uveal trabecular endothelial cells which are morphologically distinguishable from corneal endothelium. The frequency and size of the gaps between the inner uveal trabecular endothelial cells increase and are well developed by 18–20 weeks, clearly providing a route of communication between the fetal anterior chamber and the developing intercellular spaces in the primitive trabecular tissue. The implications of these observations on the 'Barkan's membrane' theory of congenital glaucoma are discussed.

There have been several hypotheses on the cause of congenital or primary infantile glaucoma. The suggestion that obstruction to aqueous humour drainage from the anterior chamber was due to a semitransparent cellular membrane which had failed to regress normally from the iridocorneal angle was proposed by Barkan.¹ The concept of 'Barkan's membrane,' which was based on gonioscopic observations, found favour among surgeons.^{2,3} However, histopathological studies could not confirm its presence.^{4,5} Further support for the membrane theory was the notion that the human fetal chamber angle is normally lined by a complete layer of cuboidal corneal endothelial cells until late in development. The timing of the normal perforation or 'regression' of this membrane, which has been suggested as 28–32 weeks,^{6,7} or in the last few weeks before birth,^{8–10} appears to have found general acceptance and is often quoted in textbooks and reviews.^{11–14} However, some authors believe that such a continuous lining exists neither in the normal fetal eye nor in cases of congenital glaucoma.^{4,5}

Although it is now over 30 years since Barkan first made his proposal, confusion still exists in this area. This is due partly to the restricted number of ultrastructural studies which have specifically addressed the nature and developmental changes in the lining of the primitive trabecular meshwork in the normal human chamber angle. Previous investigations have often been limited in the number¹ or the age range^{4,5,15} of fetal eyes available for study. To the author's knowledge there has been only one previous scanning electron microscopic (SEM) study of the lining of the chamber angle in human fetal eyes.⁶ In a previous light microscopic and ultrastructural investigation¹⁷ the present author has described the pre- and post-natal development of the lining of the human anterior chamber angle. It was shown that in fetuses as young as 12–14 weeks old the cellular covering of the trabecular anlage is incomplete and intercellular gaps become larger and more frequent as development progresses. The aim of this paper is to present convincing SEM evidence which supports the findings of the previous study. Obtaining an unobstructed view of the angle recess, which is not normally possible, proved to be crucial to the aims of this investigation.

Table 1 Details of the human fetal eyes used in the present study

Case	Sex	Age (weeks)	Weight (grams)	Crown-rump (cm)	Crown-heel length (cm)	Heel-toe length (cm)	Globe diameter (mm)	Corneal diameter (mm)
1	F	12	24.6	8.0	11.0	1.0	4.0	2.5
2	F	13	22.6	7.5	10.5	1.0	5.0	3.0
3	F	14	33.7	9.0	12.5	1.2	5.0	2.5
4	F	14	42.4	10.0	13.5	1.4	5.5	4.0
5	M	15	55.0	9.3	—	—	5.5	3.5
6	F	15	—	10.2	—	—	—	—
7	M	15	78.0	11.2	17.0	1.7	6.5	4.5
8	M	15	60.0	11.0	15.0	1.5	6.0	4.0
9	—	15	62.4	10.0	15.0	1.5	6.0	3.0
10	F	15	74.2	11.5	16.0	1.8	6.5	3.5
11	F	16	—	12.4	—	—	—	—
12	M	16	—	13.0	—	—	—	—
13	—	17	145	14.5	21.0	2.2	9.0	4.5
14	F	18	—	15.0	22.0	2.6	10.0	4.5
15	F	18	144	15.0	21.5	2.5	8.0	5.0
16*	—	20	200	12.5	—	—	—	—
17*	—	22	400	15.0	—	—	—	—

*Neural tube defects.

Materials and methods

The fetuses used in this investigation included 15 normal and two in which neural tube defects were present. Details of the 17 cases (32 eyes) are provided in Table 1.

Gestational age was calculated from the date of last menstruation, ultrasonographic data, and morphometric data obtained at the time of termination, which was prostaglandin-induced. The fetuses were stored at 4°C until the time of enucleation, which was generally less than two hours. The eyes were immersed intact in 4% cacodylate buffered glutaraldehyde fixative (pH 7.4). After a minimum of 24 hours' fixation the eyes were carefully divided at the equator and the lens gently freed from the anterior segment without damage to the optic cup. Each anterior segment was cut into meridional wedges 1 or 2 mm in thickness. In small eyes it was possible to obtain only four or five pieces of tissue, while in older eyes up to 15 wedges of limbal tissue could be obtained. One or two pieces of tissue from each eye were reserved for scanning electron microscopy (SEM), while the others were embedded in Araldite for light microscopy (LM) and transmission electron microscopy (TEM). Tissue for SEM was osmicated, dehydrated, critical point dried, sputter coated with gold, and examined in a JEOL JSM T300 (Department of Anatomy, Glasgow University, Scotland) or a Philips 505 (Department of Anatomy and Human Biology, University of Western Australia, Perth, Western Australia). After initial examination of intact wedges of limbal tissue it was apparent that to obtain a clear view of large areas of the angle recess further

dissection would be necessary. Therefore the wedges were either further divided in the meridional plane, cut tangentially, or the primitive iris/ciliary body and

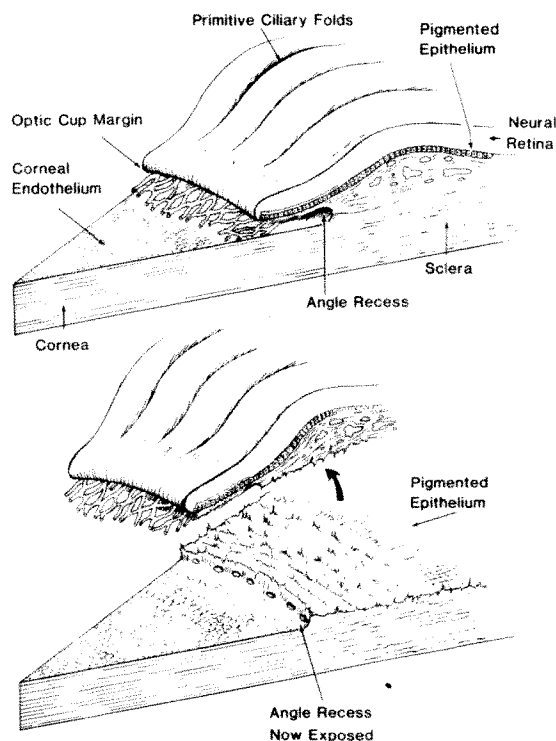


Fig. 1 Diagrammatic presentation of the dissection method used to expose the recess of the fetal iridocorneal angle for SEM studies.

neural retina were peeled gently from the corneoscleral tissue as illustrated in Fig. 1. This last procedure made a thorough examination of the transitional zone between corneal endothelium and the cells covering the angle recess possible.

Results

The anterior segment tissues of the eyes including those with neural tube defects appeared normal on macroscopic and microscopic examination. The eyes were divided into three groups for ease of description.

12–14 WEEK FETAL PERIOD

Primitive ciliary folds were not discernible by SEM on the inner surface of the optic cup at 12 or 13 weeks but became barely discernible by 14 weeks. No true 'iridocorneal angle' existed at 12 or 13 weeks, since the iris had not yet begun development. Therefore the primitive anterior chamber was limited posteriorly by loose vascular mesenchymal tissue which passed over the anterior or outer aspect of the optic cup margin to form the pupillary membrane of the tunica vasculosa lentis (Fig. 2a). The angle apex lay in an anterior position relative to the optic cup margin, while the trabecular anlage was approximately level with it at this stage in development (Fig. 2a). The collapse of the loose mesenchyme of the pupillary membrane on to the cornea made the examination of the apex of the recess difficult in undissected specimens. However, once the anterior portion of the optic cup (including primordial ciliary body and iris) was carefully removed from the wedges of anterior segment tissue as shown in Fig. 1 the true nature of the cellular lining of the angle recess became apparent.

SEM examination of the inner corneal surface distant from the angle demonstrated the character-

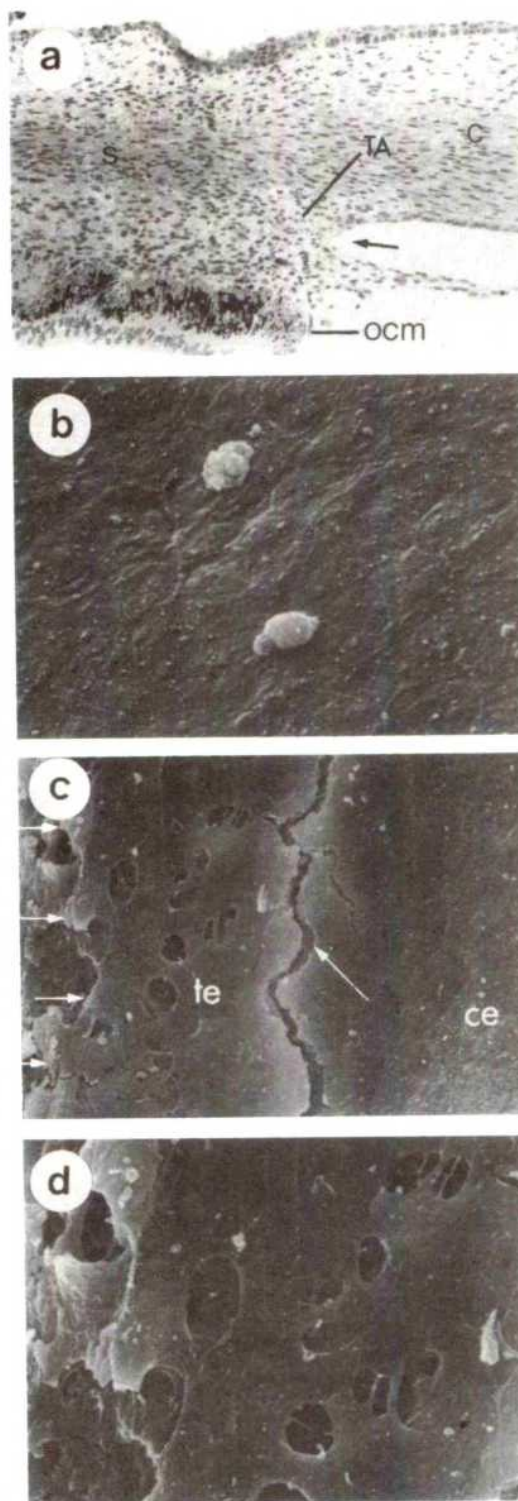


Fig. 2 Micrographs of the anterior chamber angle tissues in a 13-week-old human fetal eye. (a) Low power LM to illustrate the general configuration of the anterior segment tissues at this stage in development. c=cornea, s=sclera, ocm=optic cup margin, TA=trabecular anlage, arrow=apex of anterior chamber angle recess. (b) SEM of corneal endothelial surface showing general topography of the polyhedral cells. Note the two globular cells, probably macrophages, which are commonly associated with the tunica vasculosa lentis during development. (c) SEM of the transition zone between corneal endothelial cells (ce) and uveal trabecular endothelial cells (te). An artefactual crack (large arrow) can easily be distinguished from the intercellular gaps. The point where the tissue has separated during dissection, approximately at the angle apex, is indicated (small arrows). The gaps are shown at higher magnification in (d). Magnifications: (a) $\times 100$, (b) $\times 1200$, (c) $\times 820$, (d) $\times 1600$.

istic arrangement and surface topography of the endothelial cells, namely, hexagonal shape, slightly elevated cell borders (Fig. 2b), and often a centrally located single cilium. Within 40–50 μm of the apex of the primitive chamber angle recess the arrangement of the cells became less regular, borders were less discrete, and cilia were less obvious (Fig. 2c). These cells will be referred to as uveal trabecular endothelial cells (TECs). The thickness of corneal endothelial cells, as seen in views of the lateral cut surface, decreased near the angle apex, where they merged with the uveal TECs and ultimately with the more squamous pleomorphic cells which covered the vascular mesenchymal tissue of the iris stromal anlage. Numerous rounded or ovoid intercellular gaps with maximal diameter of 2–8 μm were usually identifiable within 20–30 μm of the apex. The openings were occasionally bridged by delicate cytoplasmic processes or filopodia (Fig. 2d). On inspection of the lateral cut surface it was evident that these gaps overlay the loose wedges of mesenchyme of the trabecular anlage.

15–17TH WEEK FETAL PERIOD

By 15 weeks of gestational age the optic cup margin, representing the primitive iris, had grown forward from the ciliary folds. The optic cup margin therefore now lay anterior relative to the apex of the irido-corneal angle (Fig. 3a,b). SEM examination of the inner surface of the optic cup (Fig. 3b) revealed smooth-surfaced simple ciliary folds, 300–500 μm long and ≈ 100 μm in width, orientated in the anteroposterior plane. A smooth-surfaced area (100–150 μm long) representing the primitive iris projected anteriorly from these folds. A distinct angle now existed between the developing iris and posterior corneal surface. The vessels passing over the optic cup margin were clearly discernible (Fig. 3b).

The typical hexagonal appearance of corneal endothelial cells (Fig. 3c) was still conspicuous to within ≈ 50 μm of the angle apex, where the transition

occurred to thinner cells with a more pleomorphic arrangement and less distinct cell margins (Fig. 3d,e). In the transitional region near the angle apex intercellular gaps were easily identified in dissected specimens. These gaps were of similar dimensions and frequency to those in the 12–14 week age group, that is, 2–8 μm in diameter. On close examination it is evident that many gaps appeared subdivided or occurred in clusters and were only partly bound by a sharp cellular border (Fig. 3e). Fine cytoplasmic filopodia often traversed the gaps. On examination of the cut surface the mesenchyme of the trabecular anlage appeared more loosely arranged.

Examination of the uncovered trabecular anlage in dissected specimens revealed bundles of circumferentially orientated collagen fibres loosely arranged among the irregular shaped mesenchymal cells.

18–22 WEEK FETAL PERIOD

Light microscopic examination of tissue from this period showed a more highly developed ciliary body and iris including the appearance of the sphincter pupillae and ciliary muscle primordia (Fig. 4a). A clear external and internal scleral sulcus were identifiable at the corneoscleral junction. SEM revealed larger ciliary folds with a more undulating epithelial surface than in younger eyes (Fig. 4b). Minor folds were now evident between the major folds. SEM examination of the angle revealed that typical corneal endothelial cells terminated more anteriorly in this age group, giving way to the more irregular uveal TECs. Intercellular gaps were now more common than in younger eyes and occasionally could be identified in undissected specimens viewed from the lateral aspect (Fig. 4c). Their shape and size range (2–15 μm in diameter) was more variable than in the younger eyes. They were regularly spaced along the inner surface of the trabecular anlage (Fig. 4d) and would obviously allow communication between the anterior chamber and the now well developed intercellular or intertrabecular spaces.

Fig. 3 Micrographs of the anterior chamber angle structures in 15-week old human fetal eyes. (a) Low power LM to illustrate the general arrangement of the tissues. Note the developing iris (compare with Fig. 2a), ciliary folds (cf) and the trabecular anlage (TA) at the apex of the angle recess (arrow). (b) SEM of a large wedge of limbal tissue in which the neural layers of the optic cup have not been removed. The difficulty of viewing the lining of the angle recess (arrow) from the lateral cut surface is clearly illustrated. (c) SEM of normal corneal endothelial cells a short distance from the chamber angle recess which demonstrates the prominent cell borders, cuboidal morphology and the primitive Descemet's membrane (dm) on their basal aspect. (d) SEM of corneoscleral tissue after removal of the neural tissue. The plane of cleavage between the neural layers and the corneoscleral tissue corresponds approximately to the arrow in (a). The line where separation occurred is clearly discernible anterior to the trabecular anlage (TA). The transition zone between corneal endothelial cells (ce) and the uveal TECs (ut) is clearly demonstrated. The intercellular gaps between the TECs are shown at higher magnification (boxed area) in (e). Note that some gaps have only one sharply delineated margin (arrow). Abbreviations (a)–(e): c=cornea; ocm=optic cup margin; ce=corneal endothelium; cf=ciliary folds; TA=trabecular anlage; pm=vessels of pupillary membrane (tunica vasculosa lentis). Magnifications: (a) $\times 430$, (b) $\times 140$, (c) $\times 2300$, (d) $\times 220$, (e) $\times 870$.

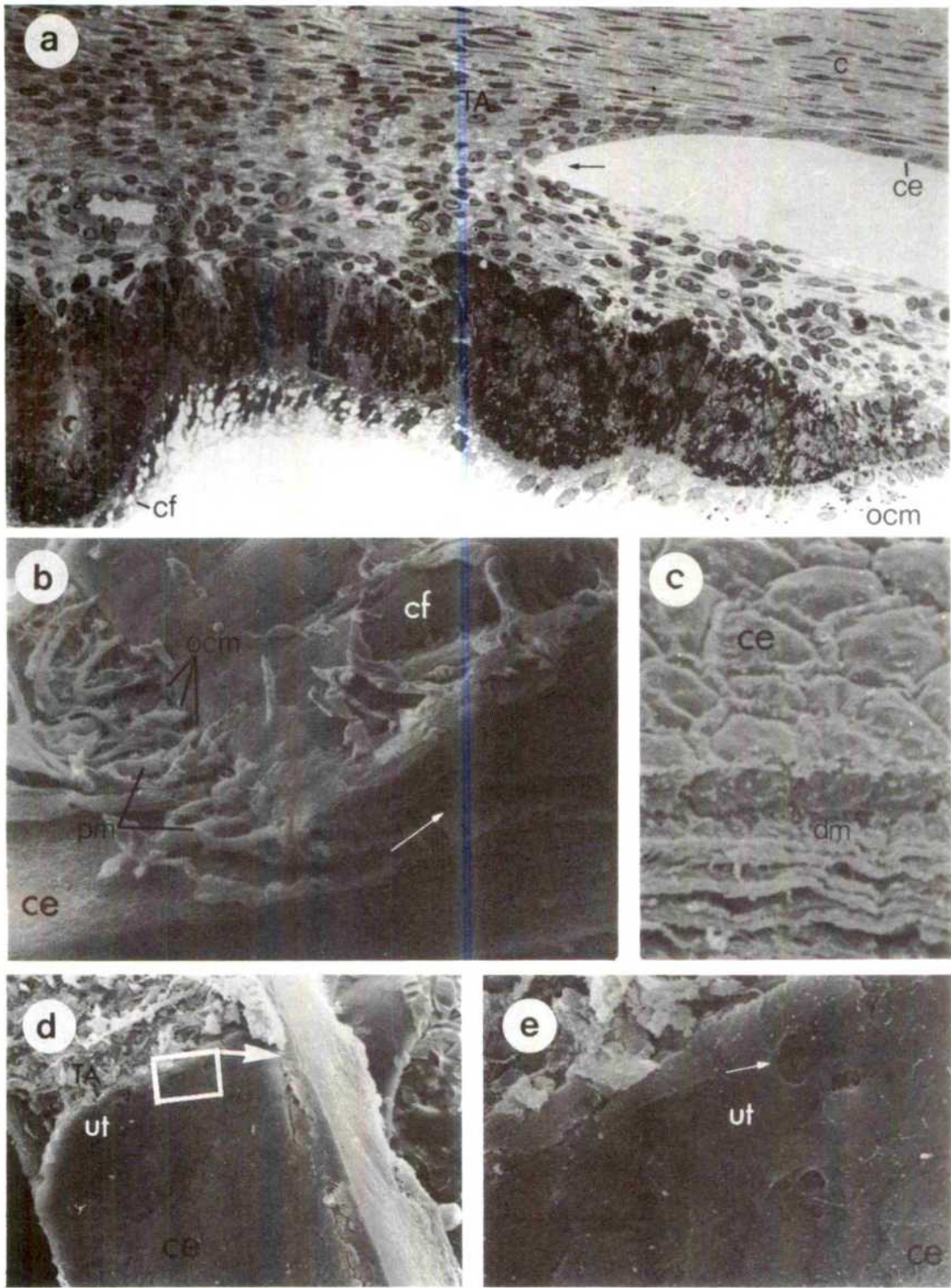


Fig. 3

Fine cytoplasmic filopodia were a more prominent feature of the uveal TECs than in the younger eyes. Only occasionally were single rounded cells with membrane ruffles, which may represent macrophages, identified close to the inner surface of the trabecular anlage.

Discussion

The present scanning electron microscopic study of the cellular lining of the anterior chamber angle is part of a comprehensive investigation of the normal prenatal development of the human aqueous outflow pathways. Earlier observations made by the present author¹⁷ at the LM and TEM level refute the suggestion of previous investigators^{19,15,16} that the inner surface of the meshwork is lined by a continuous layer of endothelial cells until late in development. The aim of the present study was to provide supplementary evidence by an additional more appropriate method (SEM) of examining the uveal meshwork inner surface. However, during examination of the lateral cut surface of meridional slices of limbal tissue difficulty was experienced in obtaining a clear view of large enough areas of the cellular covering of the chamber angle recess. Furthermore the view was often totally obscured by the tendency of the loose vascular iris mesenchyme and pupillary membrane to collapse over the angle. With appropriate care the inner neural tissues of the optic cup (retina, ciliary folds and iris) and some mesenchyme could be gently separated from the underlying corneoscleral tissue in the dried specimens (Fig. 1). Fortunately the tissue usually split at the angle apex exposing the inner surface of the trabecular anlage. As previously pointed out by Kupfer,¹⁸ the weak forces between the inner neural tissues and the outer corneoscleral layers which facilitated such damage free separation could easily be misinterpreted as a plane of 'cleavage', as indeed occurred in earlier histological studies.¹⁹ In the present study dissection or shrinkage artefacts, almost unavoidable hazards of SEM preparation, were easily differentiated from the smooth edged ovoid or round intercellular gaps in the lining of the trabecular anlage. The advantages of SEM examination of tissues dissected in this manner exceeded

the limitations described, since it allowed a true appreciation of the size, shape, and frequency of the intercellular gaps over a large area of tissue. This information could otherwise be accrued only by tedious serial section studies.

SEM observations of tissue prepared in the manner described provides convincing corroboratory evidence that there are extensive channels of communications between the fetal anterior chamber and the developing intertrabecular spaces via gaps in the cover of uveal trabecular endothelial cells as noted in a previous study.¹⁷ Intercellular gaps, while becoming more common by 18–22 weeks, were a consistent feature even in 12–14 week old fetal eyes. One limitation of the present investigation was the unavailability of material older than 22 gestational weeks. Presumably, however, the gaps would continue to increase in size and frequency in this period to reach the infant configuration.¹⁷

The only previous SEM investigation of the inner surface of the human fetal aqueous outflow system⁹ claimed that the angle was covered by a continuous monolayer of endothelial cells until the eighth month of development, though no evidence was provided, making comparison with the present study difficult. Intercellular gaps deep in the angle recess, only truly apparent in the present study after dissection, may have been hidden in the specimens examined by Hansson and Jerndal.⁹ Surprisingly, no details of the numbers or ages of specimens were provided by these authors. It is difficult to reconcile why previous ultrastructural⁷ and light microscopic^{16,22} studies have claimed that the trabecular surface has a complete endothelial covering until the seventh or eighth month of development when clearly the present SEM and previous LM and TEM evidence¹⁷ show large numbers of sizeable intercellular fenestrations or gaps. Some previous investigators, more in accordance with the present study, have considered the inner surface of the trabecular anlage to be covered by loosely organised layers of mesenchymal or trabecular cells,²³ though these studies have either not included younger eyes⁴ or have failed to emphasise the nature and extent of the intercellular gaps in early fetal eyes.²³

In an SEM investigation of the iridocorneal angle

Fig. 4 Micrographs showing iridocorneal angle structures in human fetal eyes between 18 and 22 weeks of age. (a) Several important features are now identifiable by LM in the 22-week old specimen including ciliary processes (cp), sphincter pupillae muscle (sp), ciliary muscle (cm), trabecular anlage (TA), canal of Schlemm (SC). Corneal endothelial cells (cc) terminate at the anterior limit (arrow) of the trabecular anlage. (b) Low power SEM of 20-week old fetal tissue. (c) A lateral SEM view of the cut surface of the undissected iridocorneal angle recess in an 18-week old eye to demonstrate one or two intercellular gaps (arrow). These are much more clearly seen once the iris/ciliary body complex has been removed by dissection as in (d). This plan SEM view of a 20-week old eye illustrates the abrupt transition between corneal endothelium (cc) and uveal TECs and the now very numerous intercellular gaps. Magnifications (a) $\times 160$, (b) $\times 80$, (c) $\times 1300$, (d) $\times 1800$.

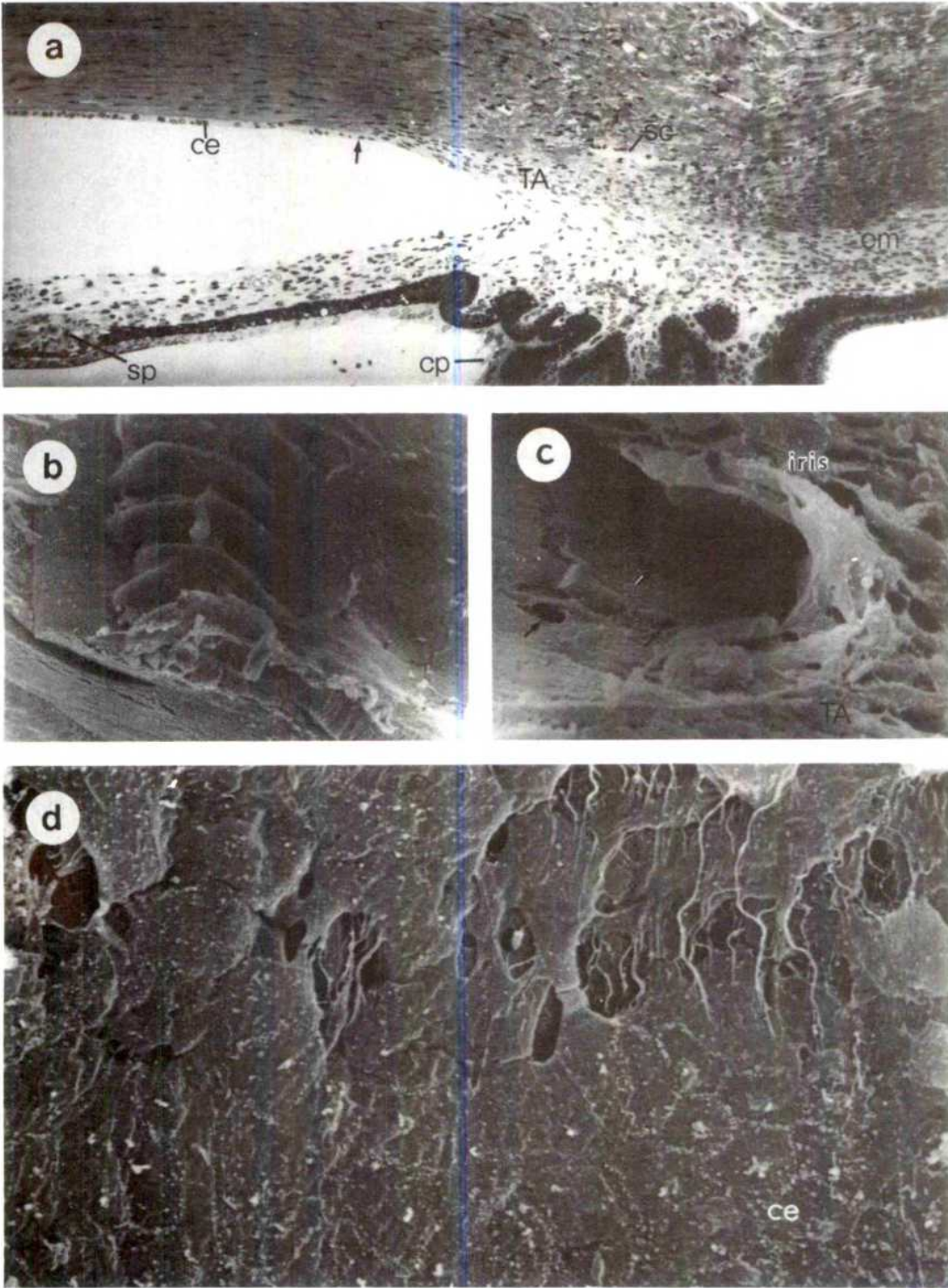


Fig. 4

development in macaques Van Buskirk¹⁰ identified small intercellular gaps in the lining in the first trimester, whereas by the second trimester only the anterior half to two-thirds of the trabecular meshwork was covered by intact endothelium. Despite evidence of gaps, as in the present study, this was interpreted as further support of late regression of a pretrabecular membrane in the normal fetal eye. Since many species of non-human primates retain an operculum and lamellate uveal trabeculae into adult life^{20,21} one would perhaps expect different remodelling events in development. Therefore the appearance in the human of relatively large and numerous gaps may be an important species difference of functional significance.

The presence of openings in the chamber angle lining early in gestation correlates with physiological evidence that some degree of aqueous drainage is effective by 17–18 weeks of fetal life²² and gradually increases during development.⁶ Indeed channels of communication between the anterior chamber and the trabecular anlage may be vital to the normal formation or cavitation of intertrabecular spaces, which were evident in the uveal layers as early as 12–14 weeks in the present study. In a study of the developing cat angle Richardson *et al.*²³ correlated increased volume of the intertrabecular spaces with the appearance of perforations in the 'membrane' which temporarily covers the meshwork.

The concept of an uninterrupted endothelial membrane (Barkan's membrane) lining the trabecular anlage during normal development has found support among clinicians who envisage an abnormal persistence or failure of perforation of this membrane to be a likely cause of obstruction to aqueous outflow and therefore of congenital glaucoma.^{1,3,9,10} Disruption of such a membrane during goniotomy or trabeculotomy appeared to correlate with a clinically demonstrable increase in aqueous outflow.² In contrast, histological evidence of a membrane continued to elude pathologists.^{4,5,15} This was considered by supporters of the membrane theory to be due to difficulties in obtaining suitable eyes at the early stages of the disease or to disruption of the membrane during processing.³ There are many theories on the aetiology and pathogenesis of congenital glaucoma including failure of atrophy or cleavage; defective neural crest cell migration; and excessive formation of collagen which prevents the normal posterior sliding of the ciliary body.^{13,14,26,27} On the basis of the present evidence it is clear that these explanations should no longer include failed regression of a complete endothelial pretrabecular membrane, since even in the early fetal eyes openings were present which appear of sufficient frequency and size to allow unimpeded egress of aqueous from

the anterior chamber. Alternative explanations of Barkan's membrane may include condensed pectinate ligaments, excess proteoglycans on the inner surface of the meshwork (W R Lee, personal communication), or the formation of secondary pretrabecular membranes due to corneal endothelial downgrowth.

Theories on the aetiology and pathogenesis of primary congenital glaucoma and other developmental abnormalities of the anterior segment, such as the iridocorneal endothelialisation (ICE) syndromes, should take the common neural crest origin of the ocular mesenchyme into account. These cells give rise to corneal stroma, corneal endothelium, iris stroma, ciliary muscle, ciliary body connective tissue, and trabecular endothelial cells. Vascular endothelial cells, and therefore presumably the endothelium of Schlemm's canal, arise independently from mesoderm. This information has been elucidated in birds by means of chick/quail chimaera and autoradiographic studies (see Noden²⁸ for review). Although definitive proof in mammals of a comparable ontogeny is still not available, it seems likely especially since craniofacial abnormalities are often associated with anterior segment dysgenesis, including congenital glaucoma.^{13,14,26,27} Theories of delayed maturation as the cause of congenital glaucoma need not be restricted to the inner or uveal portion of the meshwork. Equally important morphogenetic and remodelling events are occurring throughout the aqueous humour outflow system which if disturbed could have serious functional consequences. These developmental changes will form the basis of future reports.

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Carotid arteries in central retinal vessel occlusion as assessed by Doppler ultrasound

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SUMMARY Doppler ultrasound was used to detect possible flow changes in the carotid arteries of patients with central retinal artery and vein occlusion. Twenty-three patients with central retinal artery occlusion (mean age 56, SD 11, years) were examined 4 to 48 months after the development of the occlusion and compared with age and sex matched control subjects with no history of any disease known to be associated with pathological changes in carotid vessels. Significant stenosis or occlusion of one or more carotid arteries was discovered in eight patients with retinal artery occlusion, while the ultrasonic findings were normal in all the controls ($p < 0.005$). Blood flow was evaluated by the same method in 16 patients with central retinal vein occlusion (mean age 57, SD 9, years) six to 48 months after the event. A control group was chosen according to the same criteria as in previous comparison. Pathological ultrasonic findings were observed neither in the patients with retinal vein occlusion nor in the control group. The results suggested a possible aetiological relation between pathological changes in the carotid arteries and occlusion of the central retinal artery, but not occlusion of the central retinal vein.

The pathogenesis of central retinal artery occlusion (CRAO) is based on a few case reports and observations of the natural course of the disease. Since most of the patients are more than 60 years old, it has been presumed that in most cases CRAO is the consequence of thrombosis or embolism.^{1,2} Angiographic demonstration of thrombosis of the internal and external carotid artery, with the thrombus extending into the ophthalmic region, has been an occasional finding.³ On the other hand embolism of the retinal arteries has for long been confirmed by post-mortem examination as a possible complication of the stenosed internal carotid artery.⁴ Some clinical reports describe patients with carotid artery disease who suffered an embolism of the retinal artery.^{5,6} Occasionally retinal embolism is provoked by diagnostic and therapeutic interventions on an atherosclerotic carotid artery.²

The pathogenesis of central retinal vein occlusion (CRVO) is even less well understood and has been attributed to diminished blood flow⁷ or to a thrombotic diathesis.^{8,9} It has been presumed

that an abnormal carotid artery flow and a reduced ophthalmic arterial perfusion pressure play a significant part in the development of retinal venous changes. Atherosclerotically stenosed internal carotid or retinal arteries may slow down the blood flow through the retinal veins by a siphon effect and therefore establish conditions that are favourable for the development of venous thrombosis. Some clinical reports¹⁰ and experimental data¹¹ drew attention to the connection between carotid artery disease and CRVO. According to these speculations the cause of both CRAO and CRVO might partly originate in the diseased arteries that supply the eye.

Since occlusion of a central retinal vessel is not rare, it is rather surprising that there has been no systematic study on the state of the carotid vessels in these patients.

In the past few years we have treated 29 patients with CRAO and 16 with CRVO with streptokinase. The results have already been published.¹² The aim of the present study was to reinvestigate these patients and examine their carotid arteries by the Doppler ultrasound technique to check whether retinal vessel occlusion (CRAO or CRVO) could be considered as a marker of symptomatic carotid artery stenosis.

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Patients and methods

PATIENTS

Between 1979 and 1985, 29 patients with CRAO and 16 with CRVO were admitted to our department to receive streptokinase treatment. The diagnosis of CRAO and CRVO was confirmed by an ophthalmologist using well known criteria.¹³ In brief, CRAO was defined as a sudden and severe visual impairment to 0.1 or less, accompanied by ischaemic oedema of the retina and narrowing of retinal arteries. Direct ophthalmoscopic evidence of arterial embolism was found in only one patient. The duration of symptoms before the institution of fibrinolytic therapy was 2.5 to 24 (mean 9.5) hours in 20 patients and 1.2 to 14 (mean 4.3) days in nine patients. CRVO was defined as a severe visual impairment to 0.2 or less, accompanied by venous engorgement, numerous intraretinal and peripapillary haemorrhages, and cotton-wool spots. The duration of symptoms before the institution of fibrinolytic therapy was two hours in one patient, and 1 to 14 (mean 6.1) days in 15 patients.

It should be stressed that only patients eligible for thrombolytic therapy were included. Therefore these series represented selected patients (with either CRAO or CRVO) who had none of the following contraindications for thrombolytic therapy: active internal bleeding, cerebrovascular accident or operation within two months, any major operation, organ biopsy, puncture of non-compressible blood vessel, postpartum period, thoracocentesis, paracentesis, lumbar puncture, recent serious trauma, cardiopulmonary resuscitation (within 10 days of onset of these conditions), uncontrolled severe hypertension, coagulation defects, and age over 70 years.¹⁴

Between the previous study¹² and present study three patients with CRAO died, the cause of all deaths being stroke. In addition three patients with CRAO were unwilling to participate.

Among 23 patients with CRAO (mean age 56 (SD 11) years) there were six women and 17 men. They had suffered CRAO four to 48 (mean 29) months before the present study. Some of them had symptoms of atherosclerosis before the onset of CRAO: four patients had myocardial infarction; one of these also suffered a stroke, and a second one had his leg amputated because of gangrene. In the time between the diagnosis of CRAO and this study two further patients suffered transitory ischaemic attacks and one had a second stroke, while the patient with peripheral arterial disease lost the other leg. Arterial hypertension was present in seven and diabetes mellitus in two; four patients smoked.

Among 16 patients with CRVO (mean age 57 (SD 9) years), there were six women and 10 men. They

had suffered CRVO six to 48 (mean 28) months before the present investigation. None of them had any evident clinical signs of atherosclerosis before CRVO. Between the diagnosis of CRVO and the present study angina developed in one patient. Arterial hypertension was present in seven and diabetes mellitus in 3; three patients smoked.

In the two control groups there were 23 and 16 age and sex matched patients; they had been admitted to our department for various health problems. Besides age and sex, which were the same as in the corresponding experimental groups the only criteria for inclusion were the absence of historical and clinical data of central retinal vessel occlusion, stroke, transitory ischaemic attack, ischaemic heart disease, and peripheral arterial disease. In the CRAO control group arterial hypertension was present in five and diabetes in two; four subjects smoked. Corresponding figures for the CRVO control group were four, one, and three subjects, respectively.

METHODS

The examination was performed with a bidirectional continuous-wave Doppler ultrasonic device, with 4 and 8 MHz probes (Kranzbühler 762). The examination included the determination of blood flow direction and velocity, together with wave form analysis in the common, internal, and external carotid arteries as well as in the supratrochlear or supra-orbital arteries. Flow changes in the supraorbital or supratrochlear arteries were also examined during a compression test. The criteria of 50% or higher stenosis or occlusion were followed according to Barnes and coworkers.¹⁵ The examining physician was not informed of the diagnoses of the patients and control subjects.

The differences in frequencies of pathological tests between the various groups were calculated by the Fisher's two-tailed exact test for attributive data.¹⁶

Results

In eight patients, seven men and one woman, mean age 57 (SD 6) years, with CRAO, Doppler ultrasound measurement revealed significant carotid stenosis or occlusion of one or more carotid arteries. In two patients occlusion of the ipsilateral internal carotid artery was found, together with stenosis of either the common or internal carotid artery on the contralateral side. Four patients showed ipsilateral stenosis of the internal carotid artery. The patient who had suffered CRAO of both eyes showed evidence of bilateral internal carotid stenosis. One patient fulfilled the criteria of contralateral internal carotid stenosis (Table 1).

No pathological changes were found in the carotid

Table 1 Carotid artery stenoses or occlusions in eight patients with central retinal artery occlusion (CRAO) as detected by Doppler ultrasound measurement

Sex	Age	CRAO	Pathological changes in carotid arteries
M	62	R	Occlusion of ICA R and stenosis of ICA L
M	64	R	Occlusion of ICA R and stenosis of CCA L
M	47	R	Stenosis of ICA R
M	57	R	Stenosis of ICA R
M	57	R	Stenosis of ICA R
M	55	L	Stenosis of ICA L
F	63	R+L	Stenosis of ICA R and L
M	52	R	Stenosis of ICA L

ICA=internal carotid artery, CCA=common carotid artery, R=right, L=left, M=male, F=female.

arteries of patients with CRVO and the control subjects. The difference in the incidence of pathological findings in the CRAO group was statistically significant as compared with the control group as well as with the CRVO group (Table 2).

Discussion

Evidence of a possible link between central retinal vessel occlusion and pathological changes in carotid arteries has been incomplete, because the invasive or non-invasive examinations of the carotid arteries have not been performed systematically in this disease.

In eight patients with previous CRAO Doppler ultrasound revealed haemodynamically significant stenoses or occlusions of at least one internal carotid artery, while no changes were found in the control subjects. In all patients but one the stenosis or occlusion was on the side of the affected eye. This observation coincided with the results of Cote and coworkers,¹¹ who had found that most patients with occlusion of the internal carotid artery had suffered

stroke on the side of the affected carotid artery, and only a minority had been affected on the opposite side. Our patient who had suffered two strokes showed evidence of internal carotid artery occlusion on the same side as CRAO, and stenosis of the common carotid artery on the other. Stenoses of both internal carotid arteries were discovered in the patient who had suffered CRAO of both eyes in a two-month interval.

Data from Doppler ultrasound blood flow measurements in patients with different types of retinal ischaemia are relatively rare. Ringelstein and coworkers¹⁸ described nine patients with CRAO. In five of them Doppler ultrasound measurements were normal, while in the other four an occlusion or stenosis of the carotid artery was found on the same side as CRAO and confirmed by x-ray angiography.

Three of our CRAO patients died of stroke in the interval between the previous¹² and the present study. The state of their carotid arteries was not examined, but it can be speculated that these patients would increase the proportion of CRAO patients with diseased carotid arteries. Moreover, there are two additional reasons for supposing that the true frequency of diseased carotid arteries was probably higher than that suggested from our results. The first is the diagnostic limitations of the Doppler ultrasound technique. We followed the opinion of most investigators who considered the result of the examination to be pathological only when the diagnostic criteria of 50% or greater stenosis or occlusion were fulfilled.¹⁹ Haemodynamically less significant stenoses were therefore lost with these criteria. The possibility of retinal embolism originating from ulcerated plaques, with minimal narrowing of the carotid artery, could not be excluded.

The second reason is the selection of patients in our study. Since the patients were selected not only regarding the presence of the disease, but also regarding the absence of contraindications for thrombolytic therapy, our conclusions hold true only for this subgroup of patients with no absolute or major relative contraindication for fibrinolytic treatment (age over 70 years, severe arterial hypertension, recent stroke). Several of these exclusion criteria are known to be associated with an increased incidence of atherosclerotic changes. In an unselected group of patients with CRAO a higher proportion of patients with carotid artery stenosis would probably be found.

Our results indicated that changes in the carotid arteries were associated with CRAO. This association does not prove that carotid artery disease causes CRAO, but it does at least indicate that CRAO is a marker of carotid artery disease. It is well known that patients with CRAO are also at risk for other complications of the central nervous system and

Table 2 Results of Doppler examination of the carotid arteries in patients with central retinal artery (CRAO) and vein (CRVO) occlusion and in the control group

	Pathological findings	Normal findings
CRAO group n=23	8*	15
Control group n=23	0	23
	p<0.005	
CRVO group n=16	0	16
Control group n=16	0	16
	p>0.05	

*Significantly different from CRVO group (p<0.001).

share a high mortality rate due to advanced atherosclerosis.²¹

The examination of carotid arteries in our study was performed after and not before or at the time of CRAO. Therefore this study did not provide definite evidence on the causal relationship between the carotid artery disease and CRAO. However, if not a direct embolic consequence of proximal atherosclerotic lesions, CRAO is at least a marker of widespread atherosclerotic disease in the carotid tree.

Previously no data have been available on Doppler ultrasound examination of carotid arteries in patients with CRVO. Our results showed that none of the patients with CRVO and the corresponding control group had any significant changes in the carotid arteries. They also indicated that the pathological process leading to CRVO was probably different from that leading to CRAO. The different natural courses of CRVO and CRAO also speak in favour of this suggestion: in contrast to CRAO, CRVO is not related to an increased mortality.²¹

In conclusion, we might say that the assumption examined in this study of the aetiological relation between pathological changes in the carotid arteries and CRVO can be rejected. On the other hand the association between carotid artery stenosis or occlusion and CRAO was confirmed. This finding argues for the close examination of carotid arteries in every patient with CRAO, which is in agreement with an earlier recommendation.²²

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Efficacy and safety of apraclonidine in patients undergoing anterior segment laser surgery

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SUMMARY The efficacy of 1.0% apraclonidine (para-aminoclonidine) in preventing the rise of intraocular pressure following anterior segment laser surgery was evaluated in a randomised double-masked study. Ninety-nine consecutive patients requiring laser treatment of the anterior segment were included in the study. They were randomised into two groups, one receiving 1.0% para-aminoclonidine and the other placebo (vehicle of para-aminoclonidine). The drug caused a statistically significant reduction in pressure after the laser treatment without causing clinically significant side effects such as bradycardia or hypotension.

During the past few years a number of investigators have reported that a transient intraocular pressure (IOP) rise may follow any anterior segment laser surgery such as argon laser trabeculoplasty, argon or YAG laser iridotomy, or YAG laser capsulotomy.¹⁻⁶ This rise in IOP appears to be unrelated to the type of therapy, the type of laser used, the total amount of energy delivered, bleeding, or cellular debris that occurs during treatment, or to the degree of inflammation after treatment. The IOP rose despite the use of topical ocular hypotensive or non-steroidal anti-inflammatory agents.¹⁻⁷

A rise in pressure following laser procedures is at present being treated with carbonic anhydrase inhibitors, oral hyperosmotic agents, or topical timolol, each of which may have undesirable side effects. Apraclonidine is a topical derivative of clonidine prepared by Alcon Laboratories and has minimal systemic hypotensive effects.⁸ Animal studies have shown that apraclonidine ophthalmic solution produces minimal systemic pharmacotoxic effects.

This study, which is prospective, randomised, and controlled, analyses the efficacy of apraclonidine in preventing a rise in IOP in patients undergoing anterior segment laser procedures, namely, Nd-YAG laser capsulotomy and argon Nd-YAG laser iridotomy.

Patients and methods

Ninety-nine consecutive patients who underwent anterior segment laser treatment between August 1987 and January 1988 at the Vision Research Foundation, Madras, India, were prospectively studied. The following criteria determined exclusion from participation in the study: (1) active ocular infection or inflammation; (2) any past or present severe ocular pathology apart from cataract and glaucoma; (3) unstable cardiovascular disease which may be adversely affected by an α -adrenergic agonist, such as labile hypertension and history of stroke; (4) any abnormality preventing reliable applanation tonometry; (5) pregnant or nursing women and women of childbearing potential; (6) participation in any other investigational drug study within past 30 days; (7) patients with vision in one eye only; (8) patients taking systemic clonidine.

Approval for the study was obtained from the Ethics and Research Subcommittees of Vision Research Foundation, Madras, India. After informed consent had been obtained, at a prestudy examination a medical history was taken, ocular examination carried out, and heart rate and blood pressure recorded. The patients were then randomly assigned to either treatment (1.0% apraclonidine) or placebo groups (vehicle of apraclonidine). Only one eye of each patient was included in the study. Neither the patient nor the investigator was aware of the treat-



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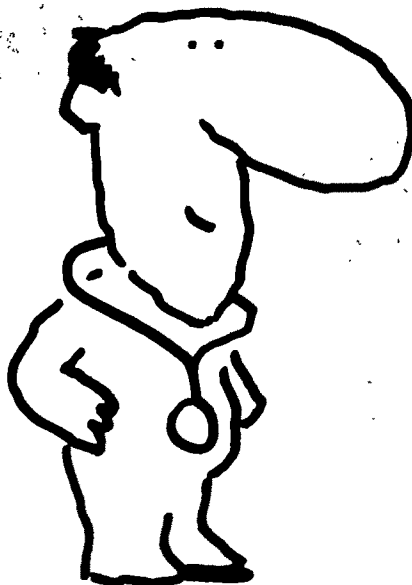
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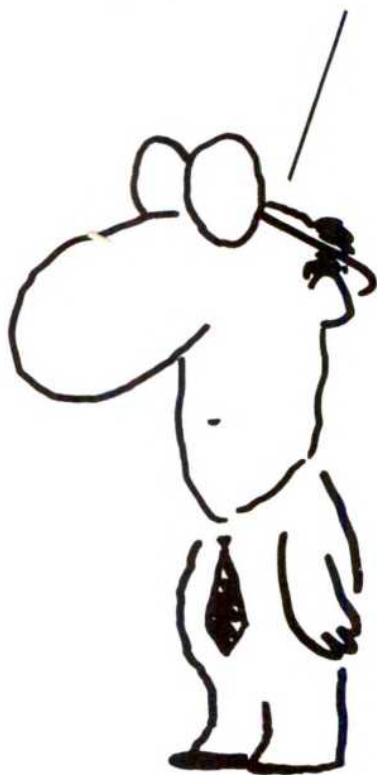
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1982; 94 (3): 318-327. 2. Rakofsky S.I. *et al.*,
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Table 1 Age and sex groups: 1 (Apraclonidine) and 2 (placebo)

Age group	Group 1 (Apraclonidine)			Group 2 (placebo)		
	Male	Female	Total	Male	Female	Total
<20	—	—	—	—	—	—
20–40	3	1	4	6	3	9
41–60	23	11	34	14	14	28
61–70	9	1	10	8	6	14
>70	—	—	—	—	—	—
Total patients	35	13	48	28	23	51

ment instituted. One drop of the test medication (1.0% active drug or placebo) was applied to the operative eye one hour prior to the laser procedure and immediately after it. The ocular examination and heart rate and blood pressure measurements were repeated hourly during the first three hours after operation and again one week later. After the laser treatment the patients continued their usual ophthalmic medication, with the addition of betamethasone 0.1% drops four times daily for four days. Additional antiglaucoma medication was administered as needed in those patients who had a rise of IOP.

The laser procedures were carried out as follows:

Nd-YAG laser posterior capsulotomy. This was done under topical anaesthesia with the minimum energy settings and pulses required to create at least a 2 mm central opening in the posterior capsule. The eye was not dilated prior to treatment unless necessary. If the eye had to be dilated, the IOP was measured one hour after the dilatation and just prior to laser therapy.

Argon Nd-YAG iridotomy. This was done under topical anaesthesia. Argon laser (blue-green) was applied with a 50 μ m spot, 0.2 second duration, power 500 milliwatts. The laser pulses were focused at a peripheral superior nasal crypt if possible. The number of applications varied from 10 to 100 to stretch the iris and coagulate the vessels. The patient was then moved to the Coherent Nd-YAG laser 9900. The previously treated site was focused with energy level of 4 to 6 mJ in one or two burst modes. A total of 5 to 200 applications were made to produce an adequate iridotomy. The patency was checked to ensure at least a 50 μ m opening. If the iridotomy closed in the follow-up period and the patient needed further laser treatment, he did not receive the test drug during this further procedure.

For the evaluation of the efficacy of the drug, the data from the two procedures were pooled. Data collected from this study was analysed as follows:

Demographic data for each treatment group were compared by two-way analysis of variance (ANOVA) for age and χ^2 for sex, ophthalmological procedure,

and ophthalmological diagnosis. A test of normal deviate was carried out on pretreatment intraocular pressures.

Analysis of data from patients with a significant rise in IOP, namely 10 mm, or more than 10 mm from the baseline, or elevation >40% of pretreatment IOP, was done by the χ^2 test. The mean difference in the blood pressure and heart rate between the two groups was analysed by the paired *t* test. For all analyses a *p* value >0.05 was considered statistically significant.

Results

Demographic data from the 99 patients evaluated in this study are shown in Table 1. There were no statistically significant differences (*p*>0.05) between treatment groups by age (Table 1), sex (Table 1), or in the mean baseline intraocular pressure (Table 2). Seventy patients underwent the laser iridotomy procedure and 29 required laser capsulotomy (Table 3). The lens status of patients enrolled for laser capsulotomy is given in Table 4, showing similar distributions between treatment groups (*p*>0.05).

Table 2 Pretreatment IOP

IOP in mm Hg	Group 1 (Apraclonidine)	Group 2 (placebo)	Total
<10	7	4	11
10–15	30	29	59
16–20	8	13	21
21–25	2	3	5
26–30	1	1	2
>30	0	1	1
Total patients	48	51	99

Table 3 Laser procedures performed

	Group 1 (Apraclonidine)	Group 2 (placebo)	Total
Capsulotomy	17	12	29
Iridotomy	31	39	70
Total patients	48	51	99

Table 4 Features in patients who underwent capsulotomy

	Group 1 (Apraclonidine)	Group 2 (placebo)	Total
Aphakic	12	7	19
PC IOL	4	4	8
AC IOL	1	0	1
Iris clip IOL	0	1	1
Total patients	17	12	29

PC= posterior chamber, AC=anterior chamber, IOL= intraocular lens.

Table 5 Indications for iridotomy

	Group 1 (Apraclonidine)	Group 2 (placebo)	Total
Chronic angle closure	16	31	47
Fellow eye	12	7	19
Pupil block: other causes	3	1	4
Total patients	31	39	70

The majority of patients requiring laser iridotomy presented with chronic angle closure glaucoma (Table 5) with the overall distribution of patients between treatment groups being statistically similar ($p>0.05$).

EFFECTS ON POSTLASER IOP

Although the baseline IOP was not statistically different between treatment groups (Table 2), the mean IOP decreased with apraclonidine treatment and increased with placebo treatment during the three hours following laser therapy (Fig. 1; $p>0.05$). The distribution of IOP changes from the prelaser baseline are shown in Table 6. The mean IOP after laser treatment was generally decreased with apraclonidine and increased with placebo

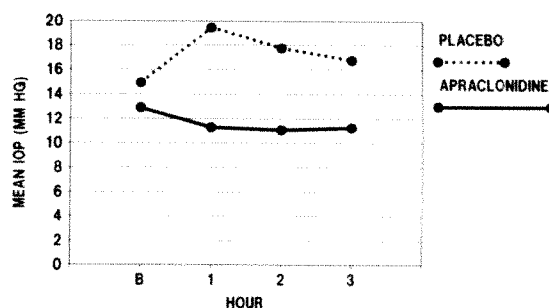


Fig. 1 Effect on intraocular pressure.

($p<0.05$). Significant severe elevations in IOP following laser treatment (that is, IOP spike equal to or greater than 10 mm Hg above the pretreatment baseline or greater than 40% above the pretreatment baseline) occurred in 52% (27/51) of patients in the placebo group and in 10% (5/48) of patients in the apraclonidine group (Table 7; $p<0.05$). At one week after laser therapy the IOP was not statistically different between treatment groups.

EFFECTS ON CARDIOVASCULAR PARAMETERS

Clinically significant effects on heart rate or blood pressure were not observed in patients from either treatment group at any time. In the three hours following laser treatment, however, some statistically significant findings unrelated to treatment were observed. The mean heart rate (Fig. 2) and systolic blood pressure (Fig. 3) were both statistically decreased from the prelaser baseline in both treatment groups ($p<0.05$). Statistical changes in diastolic blood pressure were not found (Fig. 3).

Discussion

These results confirm other preliminary reports which

Table 6 IOP changes after laser treatment

Pressure changes in mm Hg	Group 1 (Apraclonidine)			Group 2 (Placebo)		
	1 Hour	2 Hours	3 Hours	1 Hour	2 Hours	3 Hours
Pressure elevation						
1-4	8	4	9	8	16	17
5-9	5	4	3	13	10	10
10-13	0	1	2	10	3	2
>14	0	0	0	4	3	2
Pressure decrease						
1-4	25	23	21	9	10	10
5-9	6	8	6	3	3	2
10-14	0	1	2	1	2	2
15-16	1	0	0	0	0	1
>17	0	1	1	1	1	1
No change	3	6	4	2	3	4

Table 7 Significant IOP increase after laser treatment

Procedure	Amount of increase	Group 1 (Apraclonidine)	Group 2 (placebo)
Capsulotomy	≥ 10 mm above baseline	1	3
	$>40\%$ above baseline	1	1
Argon-YAG Iridotomy	≥ 10 mm above baseline	1	14
	$>40\%$ above baseline	2	9
Total patients		5	27

describe the effectiveness of apraclonidine in controlling postlaser IOP rises after laser trabeculoplasty, laser iridotomy and laser capsulotomy procedure.^{6,12} Unique to our study are the inclusion of patients with chronic closed-angle glaucoma and the combined use of the argon and Nd-YAG lasers to create iridotomies. Patients with chronic angle closure glaucoma had partial closure of the angle, and the iridotomy was done to prevent total closure of the angle. The use of both the argon and Nd-YAG lasers helped us to create iridotomies in the dark brown and thick irides seen in Indians. Our initial problems of not being able to create an adequate iridotomy with argon laser alone and the frequency of bleeds with the Nd-YAG alone have been overcome by this combined technique. Significant IOP elevation following anterior segment laser surgery can cause loss of fixation in patients with advanced glaucoma.¹

Results from the short-term evaluation of apraclonidine provide evidence supporting the efficacy of this drug in preventing a rise of IOP after anterior segment laser procedure. No adverse experiences were noted in any patient throughout the course of the trial which could be attributed to the study drug; clinically significant differences in the heart rate measurements between the two groups were not observed. Thus topically administered apraclonidine appears to influence anterior chamber dynamics with minimal systemic effects.¹³ Further

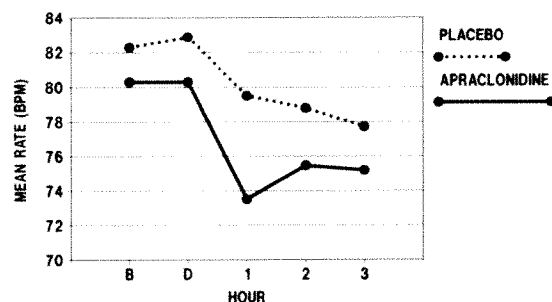


Fig. 2 Effect on heart rate.

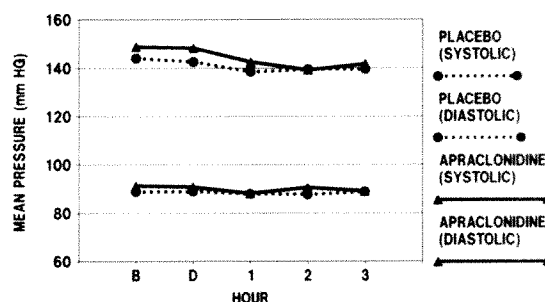


Fig. 3 Effect on blood pressure.

studies must be done to evaluate it as a topical antiglaucoma medication for more prolonged use.

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Eye injuries: a prospective survey of 5671 cases

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SUMMARY 5671 patients with injuries presenting to a busy eye casualty department were examined prospectively to determine the incidence, aetiology, and severity of the injury. Of these cases 69.9% occurred at work, 18.3% during leisure and domestic activities (excluding recognised sport), 2.3% during sport, and 1.9% were due to assaults; contact lens injury occurred in a further 2.3%, and the cause was unknown in 5.3%. One hundred and two (1.8%) patients required admission to hospital, and of their injuries 13.7% occurred at work, 22.6% during leisure and domestic activities, 42.2% at sport, 18.6% during assault, and 2.9% from an unknown cause. Children under 10 years of age accounted for 4% of the total patients presenting, but for more than 18% of those admitted and 26% of ocular penetrations. 98.3% of all injuries involved periorbital or superficial ocular structures only. The remainder involved intraocular structures. The majority of serious injuries were contusional. There was only one case of intraocular foreign body. This indicates that, while most injuries still occur in the workplace, sport and leisure activities account for the majority of serious injuries. While most injuries do not threaten sight, they do so disproportionately in children.

Ocular trauma is a considerable cause of visual impairment¹ and utilisation of ophthalmic service resources.^{1,2} However, there is little information on the cause, incidence, and severity of eye injuries. Prevention should form the basis of management, and in order to plan strategies for protection there is a need for collection of data. In the USA recent studies indicate that eye trauma, though largely preventable, still puts a considerable burden on eye departments.³ These reports, however, reflect different leisure activities, working habits, referral patterns, and protective legislation from those of the United Kingdom. Hitherto there has been little information on the aetiology of eye injuries in the UK. Most reports in this country concentrate only on injuries which necessitate hospital admission,^{4–6} occur during a particular activity,^{7–17} involve certain age groups,^{4,18} or involve a particular type of trauma.^{19,20} Casualty based studies have not linked the severity of injury to the cause and have tended to concentrate on demographic details and utilisation of services.^{21,22}

The aim of this prospective study was to determine the incidence, aetiology, and severity of eye injuries presenting to a busy eye casualty department in the United Kingdom over a 12-month period.

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Patients and methods

This study group comprised all patients presenting with ocular trauma to the combined Glasgow Eye Infirmary and Western Infirmary Casualty Department during 1 May 1987 to 30 April 1988. A proforma was drawn up so that the data could be recorded by the nursing staff, who initially see all patients in this department. The following details were recorded from each patient: age and sex, activity at the time of injury, type of injury, and presence or absence of protective eye wear (where appropriate). Corrective spectacles (without protective lenses) were not considered as a form of protection. If admission to hospital was required, the records were identified and further details of treatment and outcome were determined.

Activity at the time of injury was classified as follows: work, domestic and leisure (occurring in the home, garden, shopping, children playing, leisure activities excluding recognised sports), sport, assault, and contact lens wear. Those in whom the injury could have been due to a variety of activities or the history was not clear were designated as unknown.

In the final analysis only the most severe injury was recorded. For example, if a patient suffered

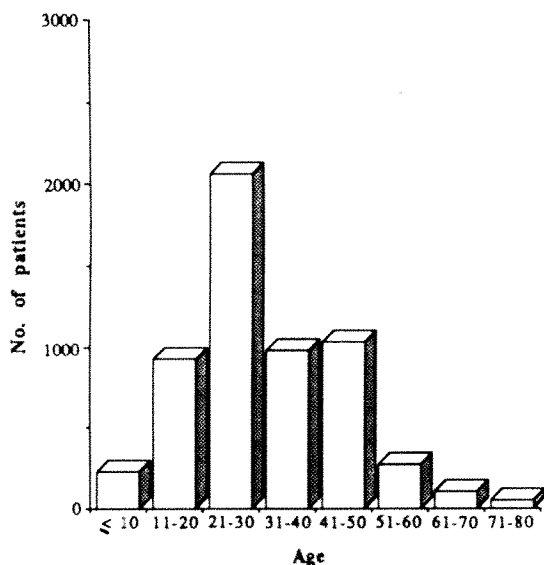


Fig. 1 Age distribution of patients presenting with ocular trauma.

hyphaema and retinal detachment, only the retinal detachment was recorded.

Results

There were 14955 new patients seen at this Casualty Department over the study period, of which 5671 presented with ocular trauma (38%). Of these, 4940 (87%) were male and 731 (13%) female. The average age was 30.6 years (range 8 months to 77 years, Fig. 1). 5440 (96%) were over 10 years of age and 231

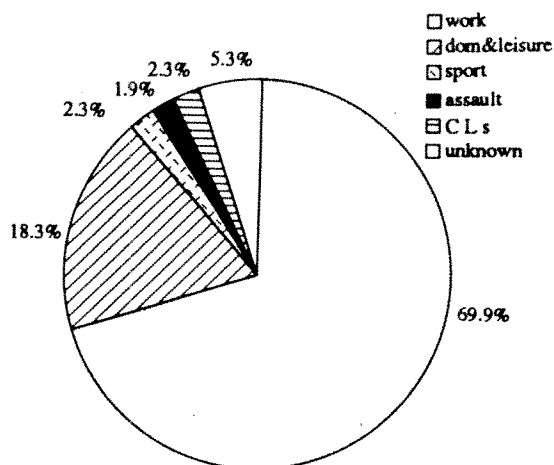


Fig. 2 Activity at time of injury in all patients presenting with ocular trauma. CLs=contact lenses.

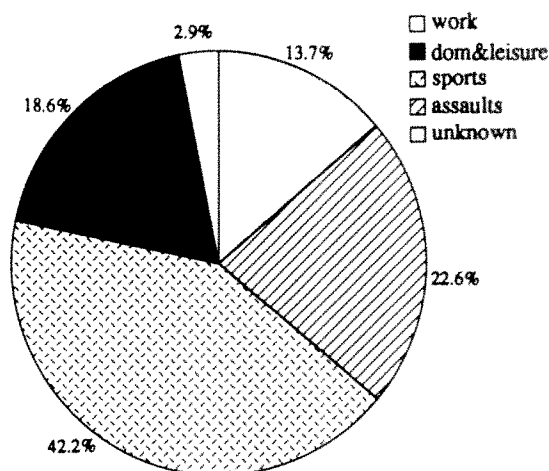


Fig. 3 Activity at time of injury in patients requiring admission to hospital with ocular trauma.

(4%) were children up to age 10. 5569 (98.2%) were treated as outpatients, of whom 1359 (24%) required at least one follow-up appointment. The remaining 102 (1.8%) were admitted to hospital; they represented 42% of the total 245 admitted cases from this department for all causes.

ACTIVITY AT TIME OF INJURY

3963 (69.9%) injuries occurred at work, 1034 (18.3%) during leisure and domestic activities (excluding sports), 131 (2.3%) during sports, and 113 (1.9%) were due to assaults. Contact lens induced injury occurred in a further 131 (2.3%). The cause of injury was unknown in 299 (5.3%) (Fig. 2).

INJURIES NECESSITATING ADMISSION

Of the 102 injuries which necessitated admission 14 (13.7%) occurred at work, 23 (22.6%) during leisure and domestic activities, 43 (42.2%) during sport, 19 (18.6%) from assaults, and in 3 (2.9%) the aetiology was unknown (Fig. 3). Of the injuries necessitating admission to hospital 19 (18.6%) occurred in children under 10 years, though they accounted for only 4% of the total patients presenting. The proportion of injuries which required admission varied according to the activity at the time of injury: 14 of 3963 (0.4%) at work, 23 of 1034 (2.5%) during domestic work and leisure, 19 of 113 (17%) from assaults, 43 of 131 (33%) during sports, and 3 of 199 (1%) in which the cause was unknown.

EXTENT OF INJURY

Injuries involving periocular tissues only numbered 156 (2.8%), of which 7 were facial or blow out fractures and 8 were lacerations which involved

Table 1 *Extent of injury occurring during different activities*

<i>Injury</i>	<i>Work</i>	<i>Domestic & leisure</i>	<i>Sport</i>	<i>Assault</i>	<i>Unknown</i>	<i>CLs</i>	<i>Total</i>
Periocular	36	47	26	47	0	0	156
EOFB	2660	208	14	4	249	0	3155
Cor. Abr.	625	580	31	30	41	98	1405
UV keratitis	431	85	0	0	1	0	517
Conjunctival	130	33	11	13	6	11	204
Chemical	69	64	0	0	0	22	155
Uveitis	4	2	12	6	0	0	24
Hyphaema	3	5	21	1	1	0	31
Disloc lens	0	0	1	1	0	0	2
Cataract	1	0	0	0	0	0	1
Post. seg.	2	1	14	4	0	0	21
Lac./rupture	1	9	1	7	1	0	19
IOFB	1	0	0	0	0	0	1
Total	3963	1034	131	113	299	131	5671

EOFB = extraocular foreign body. Cor abr. = corneal abrasion. Lac./rupture = laceration or rupture. IOFB = intraocular foreign body. CLs = contact lenses.

either the canaliculi or lid margin or caused loss of tissue, 2661 (46.9%) were corneal foreign bodies, 474 (8.4%) subtarsal foreign bodies, 1405 (24.8%) corneal abrasions, 517 (9.1%) ultraviolet keratitis, and 204 (3.6%) conjunctival lacerations or subconjunctival haemorrhages. 155 (2.7%) were chemical injuries, of which four were lime burns. There were 24 cases (0.4%) of traumatic uveitis, 31 (0.5%) hyphaemas, 1 (0.02%) cataract, and 2 (0.04%) lens dislocations. There were 21 (0.4%) cases of contusional posterior segment damage, of which 4 were of vitreous haemorrhage, 5 choroidal tears, 6 retinal holes or detachments, and 6 significant retinal oedema. There were 18 (0.3%) ocular lacerations and 1 ruptured globe (contusional). There was only 1 (0.02%) intraocular foreign body (Table 1).

INJURIES AT WORK

Injuries at work numbered 3963; 3918 (98.8%) of the patients were male and 45 (1.2%) were female. The type of work performed was grinding/buffing in 1841

(46.5%) cases, welding in 902 (22.8%), working in a dusty atmosphere or under a car in 717 (18.1%), drilling or hammering in 326 (8.2%), loading or stacking goods in 72 (1.8%), office work in 21 (0.1%), and miscellaneous in 83 (2.1%) (Table 2). The majority of injuries were superficial, corneal foreign bodies accounting for 2192 (55.3%), subtarsal foreign bodies for 468 (11.8%), corneal abrasion for 625 (15.8%), bruising for 36 (0.9%), flash burn for 431 (10.9%), conjunctival injury for 130 (3.3%), chemical burns for 69 (1.7%). 12 (0.3%) involved intraocular structures: uveitis 4, hyphaema 3, cataract 1, posterior segment damage 2, globe rupture 1, and intraocular foreign body 1 (Table 1).

No form of eye protection was worn by 3352 (84.6%) at the time of injury, though for the majority this was available; 452 (11.4%) indicated that they had not felt protection was required. 611 (15.4%) were wearing some form of eye protection at the time of injury (Table 2). No serious injury occurred at work in those who were wearing eye protection.

LEISURE AND DOMESTIC

1034 injuries occurred during leisure and domestic activities (excluding recognised sports). Of these injuries 450 (43.5%) occurred in adult men, 383 (37%) in adult women, and 201 (19.5%) in children up to 10 years. Most of these injuries were periorbital, but a significant number, especially in the younger patients caused serious sight threatening injury. Of the 23 patients admitted 17 (78%) were aged 10 or under. They had all either fallen on to or been struck by a potentially penetrating object. Seven were admitted for examination under anaesthetic, when no serious damage was found other than lid or conjunctival laceration. However, there were 5

Table 2 *Occupation at time of injury*

<i>Type of work</i>	<i>Protection not worn</i>		<i>Protection worn</i>	<i>Total</i>
	<i>Required</i>	<i>Not required</i>		
Grinding/buffing	1492	44	305	1841
Weld	683	47	172	902
Under car	408	155	74	717
Drilling/hammering	192	88	46	326
Loading/stacking	16	52	4	72
Office	0	21	0	21
Others	29	45	10	84
Total	2900	452	611	3693

Table 3 Mechanism of injury during domestic and leisure activities

Mechanism of injury	Number
Struck by or fell into large object	563
Small foreign body	302
UV light	85
Toxic material	84
Total	1034

ocular penetrations, 4 hyphaemas and 1 choroidal tear in this age group. Four of the 5 admitted adults had a lacerated or ruptured globe.

Of the superficial injuries 232 (22.4%) were caused by a child's finger scratching the eye; 84 (8.1%) patients presented with ultraviolet keratitis caused by sunray lamps, none of whom were wearing protective goggles (Table 3). There were 25 injuries from road traffic accidents, all of which were superficial. There were no firework injuries.

SPORT

Injuries during sporting activities numbered 131 (Table 4). Of these patients 43 (33%) were admitted to hospital. There were 112 (85.5%) adult males and 13 (9.9%) adult females, and 6 (4.6%) were children up to 10. The sport involved was football in 55 cases (42%), squash in 13 (9.9%), badminton in 9 (6.9%), rugby in 7 (5.3%), golf in 6 (4.6%), cycling in 5 (3.8%), swimming in 5 (3.8%), and other sports 31

(24.7%). Of these injuries 82 (62.6%) were superficial, involving the external eye or periorbital tissues, which included 2 severe lid lacerations and 4 blow-out fractures, and 49 (37.4%) involved intraocular structures (Table 4). No patient was wearing any form of eye protection when injured during sport. Of the 43 cases admitted 22 (51.1%) occurred during football, 7 (16.3%) during badminton, 4 (9.3%) during squash, 2 (4.7%) during shinty, 2 (4.7%) while fishing, and 6 (13.9%) in other sport. Sports played with a ball predominated, and the ball was responsible for injury in the majority of cases admitted. There were no boxing injuries.

CONTACT LENS INJURY

Patients with contact lens injuries numbered 131. None required admission, as all the injuries were superficial due to poorly fitting contact lenses, overwear of lenses, or incorrect use of solutions. Allergy to solutions was not considered a form of trauma.

ASSAULTS

There were 113 injuries caused by assault; 19 (16.8%) of these patients were admitted to hospital; 91 (80.5%) were male, 21 (18.6%) female, and 1 (0.9%) a child under 10. The exact nature of the assault was not always clear. Most of the injuries were periorbital; they included 2 blow-out fractures, 1 fractured malar complex, and 3 facial/lid lacerations. There were 7 cases of globe penetration, 1 of dislocated lens, and 4 of blunt trauma causing posterior segment damage.

Table 4 Extent of injury during sporting activities

Sport	Periorbital	FB	Corneal	Conj	Uveitis	Hyphaema	Post. Seg	Rupture	Total
Football	12	2	12	2	6	10	11	0	55
Squash	2	0	4	0	3	3	1	0	13
Badminton	0	0	1	0	1	6	1	0	9
Rugby	5	0	2	0	0	0	0	0	7
Golf	1	2	3	0	0	0	0	0	6
Cycling	0	2	2	1	0	0	0	0	5
Swimming	0	0	3	2	0	0	0	0	5
Other	8	1	11	3	3	2	2	1	31
Total	28	7	38	8	13	21	15	1	131

Table 5 Final visual acuities of admitted patients

Acuity	Work	Domestic and leisure	Sport	Assault	Unknown	Total
6/5-6/12	12	18	37	8	2	77
6/18-6/60	0	1	1	2	0	4
CF-HM	2	4	3	3	0	12
PL-NPL	0	0	0	2	1	3
Unknown	0	0	2	4	0	6
Total	14	23	43	19	3	102

CF=counting fingers, HM=hand movements, PL=perception of light, NPL=no perception of light.

AETIOLOGY UNKNOWN

The cause of injury was not certain in 299 patients. These injuries were largely superficial corneal abrasions or foreign bodies, and they could have occurred during a variety of activities. Three (1%) were admitted to hospital, a 2-year-old child with a delayed presentation of ruptured globe and 2 mentally retarded adults with hyphaema.

ADMITTED CASES

Of the 102 admitted patients 37 (36.3%) underwent surgical intervention. Eight had examination under anaesthetic and simply required suture of a lid or conjunctival laceration. Nineteen had corneoscleral lacerations closed, 6 had retinal detachment surgery, and 2 lensectomy-vitreotomy procedures. One intraocular foreign body was removed in combination with lensectomy-vitreotomy and corneal graft. The malar complex was elevated in one patient. Of the hyphaemas 2 bled again (no surgical intervention), 4 had a prolonged increase in intraocular pressure (1 trabeculectomy), 4 had significant residual mydriasis, and 7 had angle recession. There were no enucleations. The final visual acuities of admitted patients were good (Table 5). The length of admission varied from 1 to 44 days (mode 4 days).

Discussion

Despite the fact that eye trauma accounts for 1 in 20 cases seen by ophthalmologists,¹ many consider it has not received the attention it deserves.^{2,3} In the present study 38% of all new patients seen at this casualty department presented because of injury. This is in keeping with previous studies indicating an incidence of between 45–52%.^{21,22} It therefore takes up a considerable proportion of casualty time. 90% of eye injuries are said to be preventable, and implementation of protective legislation has been effective in certain circumstances. In 1923 (prior to the institution of British Standards for industrial eye protection), 71% of cases admitted to hospital with eye trauma were due to occupational accidents,⁴ but this had fallen to 15% by 1980.⁶ Road traffic accidents were a major source of penetrating eye injury prior to the introduction of the seat belt law in 1983^{16,19,24} but now are rarely responsible for severe eye injuries.^{6,17,19,24} The introduction of face mask protectors in ice hockey has reduced an estimated 70 000 eye injuries annually in North America.^{25,26} In the United States the National Eye Trauma System has been set up to examine the aetiology and thereby allow planning of severe eye trauma. No such data collection system exists in Great Britain, though collection of information on a nationwide scale has been attempted in certain areas.²⁷

Most reported eye injuries are superficial, but their cost in terms of health budgets and absence from work have been estimated to be enormous.² In addition, the long term outcome, especially in cases of blunt trauma, has not yet been fully established.

OCCUPATIONAL

The present study has shown that the majority of injuries still occur in the workplace, usually while the patient was carrying out light industrial tasks. Most of these injuries were superficial, but they accounted for a significant amount of time taken off work to attend the casualty department and for follow-up. At the time of injury most of the patients were not wearing any eye protection, though this was usually available. Reasons given for not wearing it were: discomfort, inability to see the task being performed, forgot, or did not feel that it was really necessary. Interestingly, many people working under cars or in dusty atmospheres thought that protection was unnecessary, and some workers remain unaware of the dangers of hammering without eye protection. 15.4% were wearing some form of eye protection, but this had failed to work adequately. The lack of efficacy of eye protection was in the main attributed to: foreign material entering the side of protective glasses, foreign material falling off protective glasses into the eyes, or ill fitting devices. Almost one-fifth of welders and grinders suffered injury despite wearing protection.

A small minority of injuries (0.4% of all work injuries) were serious enough to require the patient's admission to hospital. There was only one case of intraocular foreign body and one of globe penetration occurring at work, a proportion significantly lower than has been reported in the United States² and earlier in Britain.^{4,6} No serious injury requiring admission occurred when eye protection was in use, suggesting that existing protective eye wear is effective against severe injury. It is important to encourage the continued use of occupational eye protectors and constantly improve the devices available.

DOMESTIC AND LEISURE

This was a common source of ocular trauma, especially in women and children (accounting for 61% of all women's injuries and 87% of children's). Most injuries were superficial. The commonest causes were large objects scratching the front of the eye, especially children's fingers, domestic appliances, and toys.

Domestic cleaning fluids and cosmetics caused the majority of chemical injuries. Males commonly suffered superficial injuries during do-it-yourself tasks, car repairs, and gardening.

One disturbing feature of the injuries in this group was the number of ocular penetrations – representing almost 50% of those in the total series. Most of these injuries occurred in children up to 10. There is evidence that the incidence of penetrating injuries in children is declining,³⁸ but in this study 26% of these injuries occurred in children. Other studies have shown that children are disproportionately liable to severe eye injury.²⁴

There should be increased awareness that the home is an area in which serious eye injuries can occur, commonly in the young. Men often wear protective devices at work but fail to do so at home when carrying out similar DIY tasks.

Road traffic accidents were responsible for only a small number of superficial injuries. Ultraviolet keratitis due to the use of sunray lamps without eye filters may be an increasing problem.

SPORTS

One of the most interesting findings of this study was that, while sports accounted for only 2.3% of the total eye injuries, they were responsible for 42% of the cases admitted to hospital. This indicates that sport is now a major source of serious eye injury. 68% of all hyphaemas and 67% of posterior segment injuries occurred while playing sport, reflecting the blunt nature of the trauma. Recently it has been shown in the USA that although sport was responsible for 3.4% of eye injuries it was responsible for 60% of hyphaemas and 10% of ruptured globes in the adult population.² Studies in Britain show a similar disturbing pattern of serious eye injury associated with sport,^{8 9 12 21 29 30} despite the different types of sport played on opposite sides of the Atlantic (baseball and soft ball being the commonest causes of eye injuries in the United States). Soccer is the commonest cause in various studies in the UK,^{8 9 14} but this has largely been ignored, with most emphasis on the racquet sports played with a small ball, especially squash.^{11 12 29 30} The size of the ball is thought to be of utmost importance and anything greater than 4 inches (10 cm) in diameter should be unable to enter the bony aperture and therefore distribute its force to the periorbital tissue. This has not been borne out in fact. The football is responsible for most severe soccer injuries, and the momentum of the heavy ball causes posterior segment damage more commonly in footballers than any other sport. Scottish Sport Council figures indicate that football is four times more commonly played than squash (adult) on both a supervised and unsupervised basis (Best JP, personal communication), suggesting that injuries are equally common in both sports pro rata but the football injuries are more severe. This may reflect the use of goggles by squash players.

Development of eye protection for sporting activities which meet adequate standards with appropriate optical and visual field requirements is essential. This is not a problem with racquet sports, but the present rules of football allow no place for such protection. We must encourage players to be aware of the dangers of sport and to wear protection where appropriate. Unfortunately there is at present no British Standard, and eye protectors are not readily available because of poor demand.¹⁴

ASSAULTS

Injuries due to assaults were distributed over the whole range of injury, from minimal contusions to extensive disruption of the globe. This was the commonest cause of ocular penetration in adults and was responsible for the most devastating visual loss. Assaults are commonly cited as a common cause of serious eye injury,²⁴ but the circumstances and cause are often difficult to determine.

IMPLICATIONS AND CONCLUSIONS

The main findings of this study are that ocular trauma is a common cause of presentation to the eye casualty department. While occupational accidents still account for the majority of injuries, leisure and sport are now causing a significant number of injuries. Moreover the latter cause most injuries which require hospital admission. A disproportionate amount of serious eye injury occurs in children. The majority of serious eye injuries were contusional, with fewer perforations and intraocular foreign bodies.

It appears that there is still scope for improvement of the design and use of eye protection, especially in sport. Large surveys, preferably on a national basis, may provide sufficient data to increase public awareness and so expedite the appropriate measures.

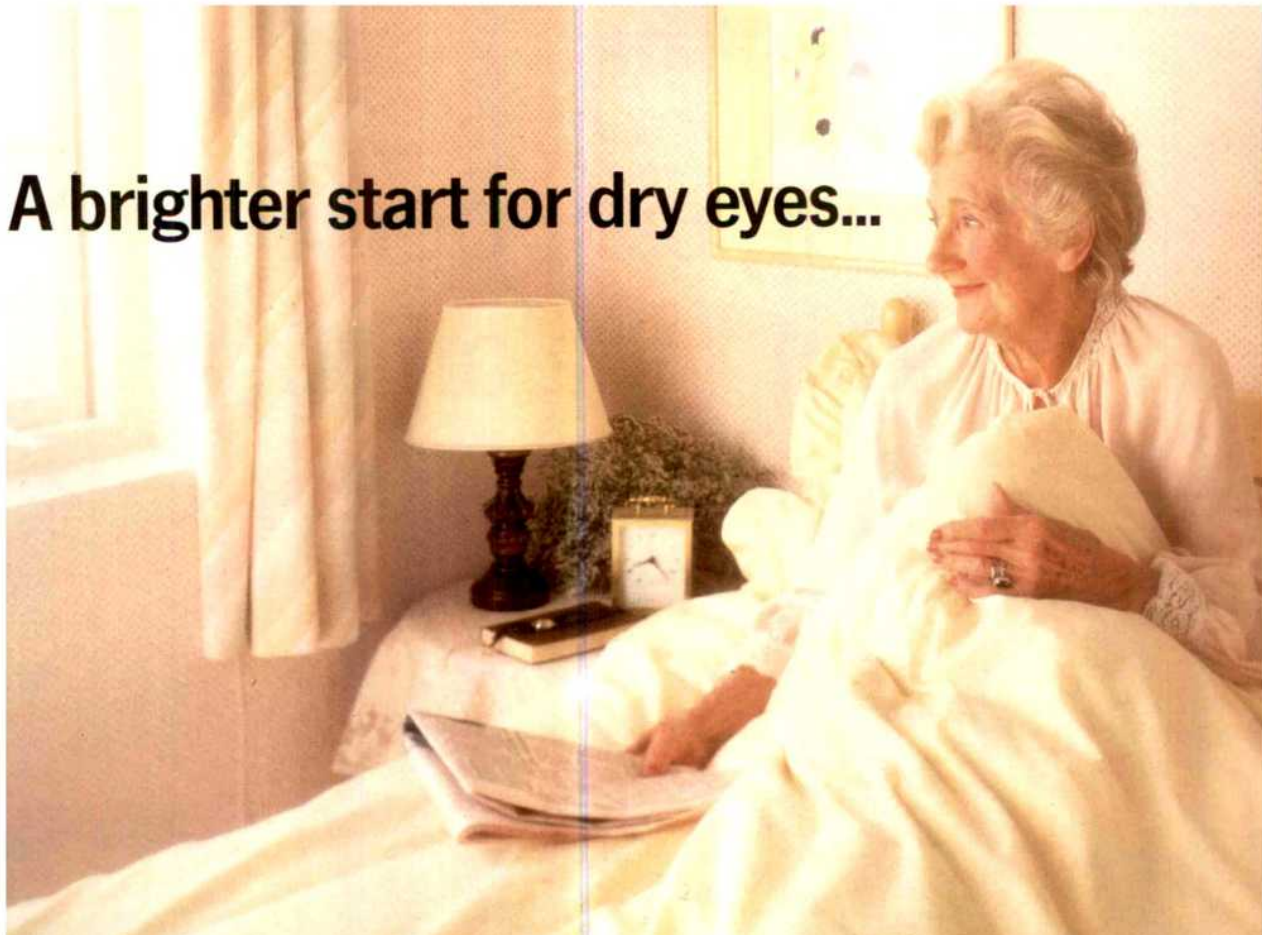
I would like to thank all the nursing staff in the Glasgow Eye Infirmary and Western Infirmary Eye Casualty Department for their co-operation and assistance and Mrs Lynda Rose for typing the manuscript.

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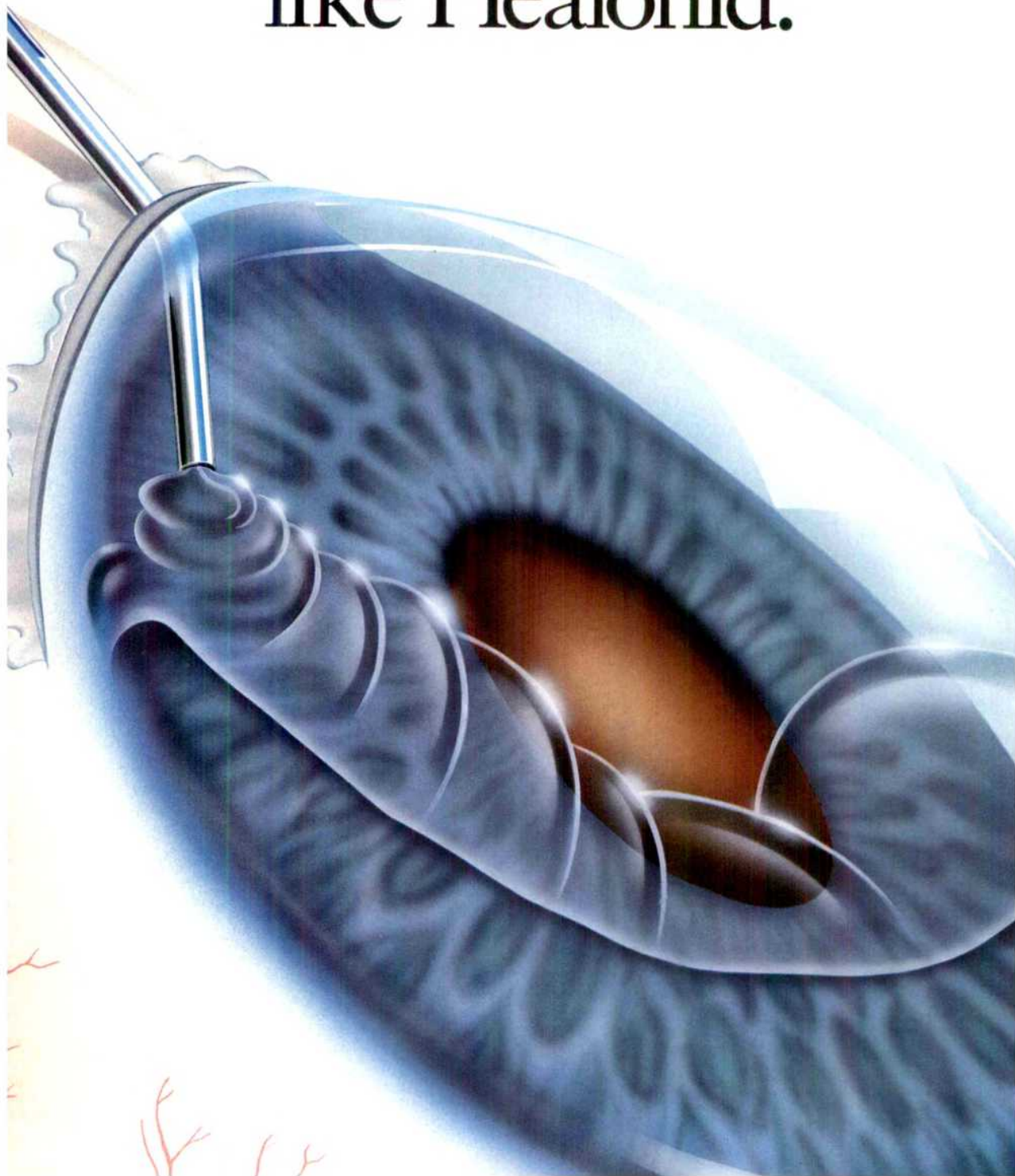
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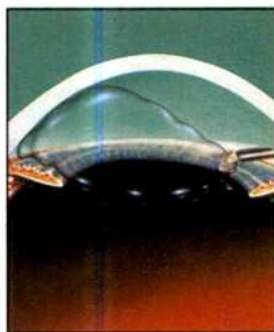
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A randomised prospective study of treatment of non-ischaemic central retinal vein occlusion by isovolaemic haemodilution

L. L. HANSEN,¹ J. WIEK,¹ AND M. WIEDERHOLT²

From the Departments of ¹Ophthalmology and ²Clinical Physiology, Klinikum Steglitz, Freie Universität Berlin, West Germany

SUMMARY In a randomised study 25 patients over 50 years of age with non-ischaemic central retinal vein occlusion (CRVO) were assigned to either a treatment (14 patients, isovolaemic haemodilution) or a control group (11 patients, no treatment). After three months eight eyes in patients with haemodilution improved, whereas none of the untreated eyes had better visual acuity ($p < 0.01$). Thirteen haemodiluted and 11 control patients could be observed for one year. Six eyes of the haemodiluted patients retained a better visual acuity, whereas no improvements had occurred in the control group ($p < 0.025$). In fluorescein angiography the lowering of the packed cell volume to 35–32% accelerated the time of maximal venous filling (t_{mvf}) from 17.4 (SEM 1.4) s to 11.4 (SEM 0.9) s ($p < 0.005$). In patients with non-ischaemic CRVO without treatment the passage time did not change. The shortened t_{mvf} reflects a higher blood velocity. Thus isovolaemic haemodilution improves the visual prognosis in non-ischaemic CRVO probably by inducing a higher blood fluidity, which results in higher blood velocity, at least in areas of compromised retinal microcirculation.

Since von Michel¹ categorised the entity of central retinal vein occlusion (CRVO) more than 100 years ago numerous experimental and clinical studies on this disease have been carried out. However, CRVO continues to lead to visual disability in most cases, especially in patients suffering from the ischaemic type,² though the most serious complication, namely, ocular neovascularisation of various types, can be prevented by panretinal photocoagulation.^{3,4}

In a randomised prospective study⁵ we showed that the visual outcome of patients with CRVO can be improved by isovolaemic haemodilution (IHD). This kind of treatment had been prompted by finding increased whole blood and plasma viscosity in patients with CRVO.^{7–9}

But, as our first study⁵ indicated that ischaemic CRVO might respond better to IHD than its non-ischaemic counterpart, we also performed this randomised trial to find out whether IHD

improves the visual outcome in patients with non-ischaemic CRVO in comparison with untreated patients.

Patients and methods

Venous obstructions may be either ischaemic or non-ischaemic. This division depends mainly on fluorescein angiographic and ophthalmoscopic criteria.^{1,10,11} We chose criteria (Table 1) that were based largely on the findings of Sinclair and Gragoudas¹² but also took into account visual acuity, which has been stressed as an important parameter for the visual

Table 1 Criteria for non-ischaemic CRVO (at least two conditions have to be fulfilled)

- | |
|--|
| (1) Fluorescein angiogram: time for maximal venous filling (t_{mvf}) < 20 s |
| (2) Capillary occlusion: area of < 1 prism dioptré and/or < 10 cotton-wool spots |
| (3) Visual acuity $> 6/60$ |

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Table 2 Entrance data of patients with non-ischaemic CRVO

	IHD	Control
Patients (n)	14	11
Women (n)	6	7
Age (years)	64.9 (SEM 2.3)	69.4 (SEM 3.2)
Duration of occlusion (days)	15.0 (SEM 4.0)	18.0 (SEM 3.0)
Initial visual acuity $\geq 6/15$ (n)	7	8
Initial visual acuity $\leq 6/60$ (n)	2	1

outcome of patients with CRVO.² Between August 1985 and December 1986 patients with non-ischaemic CRVO entered a randomised controlled study on IHD. After complete medical and ophthalmic examination they were randomly assigned by a lottery system to either control group (no treatment) or haemodilution group. However, it was not possible to treat these patients in a masked manner because the paleness of a haemodiluted patient cannot be hidden from the investigator.

Patients with systemic diseases (congestive heart failure despite treatment, renal insufficiency, and respiratory insufficiency of the pink puffer type, anaemia below 38% packed cell volume (PCV), thrombocytosis above $450 \times 10^9/l$) insufficient clarity of media, pre-existing macular disease, and psychosocial problems that would not allow an outpatient haemodilution and long-time follow-up were excluded from the study (Table 2).

Complete ophthalmic examinations (visual acuity, slit-lamp examination of the anterior segment, gonioscopy, fundus biomicroscopy, applanation tonometry, visual fields (Goldmann), colour photography of the fundus) were done before haemodilution, in the sixth and twelfth week after the beginning of treatment, and thereafter every three months up to one year.

Visual acuity was determined fully refracted at 6 m by examiners who were not involved in the study. A change in visual acuity was considered to be present if the patient could read at least two steps more or less on the scale as shown in Figs. 1 and 2. It requires a reduction of the visual angle to nearly one-half in the upper end and to about one-quarter in the lower end of the scale. This fulfils at least the conditions for visual acuity change as demanded by the Diabetic Retinopathy Study Group.¹⁵

Fluorescein angiograms were done at the patient's first presentation and repeated after two and six weeks as well as after one year. Fluorescein (10 mg/kg) was injected into the cubital vein within 3 seconds. The time from the appearance of the dye in the retinal arteries to the complete or maximal filling of the major temporal veins (t_{mvf}) was used as

indirect parameter for the flow velocity in retinal vessels. In addition the fluorescein angiograms were examined for areas of retinal capillary non-perfusion, completeness of the perifoveal arcade, leakage, and, in late stages, for intraretinal microvascular abnormalities and new vessel formation.

Haemodilution was induced as described previously.⁶ 300–500 ml of whole blood was repeatedly taken from the cubital vein. After centrifugation the plasma was separated and reinfused. The lost volume of the blood cells was immediately replaced by 150–250 ml of low molecular weight dextran (MW 40 000). Possible anaphylactic reactions were prevented by intravenous injection of 20 ml of small dextran molecules (MW 1000) as proposed by Hedin *et al.*¹⁶ During a one-week stay at hospital the PCV was reduced to 35–30% (in patients older than 75 years not below 35%). During an additional five-week period dilution was repeated on an outpatient basis whenever the PCV exceeded 35%.

The results of the statistical evaluation are expressed as mean values with standard error of the mean if not otherwise indicated. The significance of the difference between corresponding values was tested with Student's *t* test. Visual acuity changes were tested by Fisher's exact test, based on the χ^2 distribution (2×2 table).

Results

The randomised study had been planned for 40 patients, but was stopped for ethical reasons after a significant effect became obvious. So only 25 patients were enrolled in the randomised, controlled trial of the effect of IHD in non-ischaemic CRVO. Our classification was done during the first three days after the first presentation of the patient. Two of 14 eyes with non-ischaemic CRVO in haemodiluted patients converted to the ischaemic form (Table 1) in spite of haemodilution, whereas in control patients 4 of 11 eyes developed ischaemic CRVO, three of them within the first two months. These eyes underwent a panretinal photocoagulation, as has been reported elsewhere.⁶

The 25 patients were well matched on entry (Table 2) for sex, age, duration of occlusion, and initial visual acuity. All the patients could be examined after three months and only 24 patients after one year because one patient had meanwhile left the country. Whereas eight of 14 patients with IHD attained a better visual acuity after three months (Fig. 1), none of the 11 control patients had any visual improvement ($p < 0.01$). Deterioration occurred in two of the 14 haemodiluted and in four of the 11 control patients. After one year the rates of visual improvement were still the same in both groups and remained

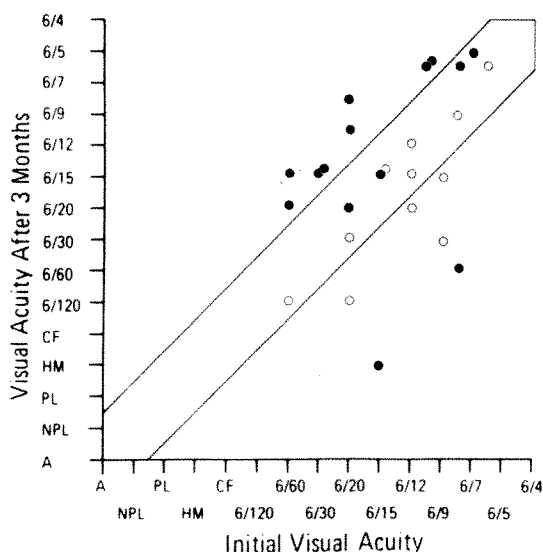


Fig. 1 Visual acuity before and three months after starting haemodilution in eyes with non-ischaemic CRVO (randomised study). Closed symbols stand for haemodiluted, open symbols for untreated eyes.

significantly different ($p < 0.025$, Fig. 2). However, five of 11 control patients versus one of 13 haemodiluted patients showed a loss of more than two lines on the test chart.

The final visual acuity may be taken as another

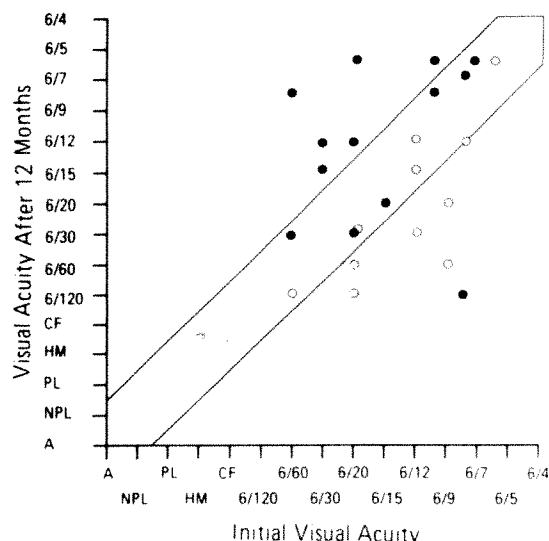


Fig. 2 Visual acuity before and 12 months after starting haemodilution in eyes with non-ischaemic CRVO (randomised study). Closed symbols stand for haemodiluted, open symbols for untreated eyes.

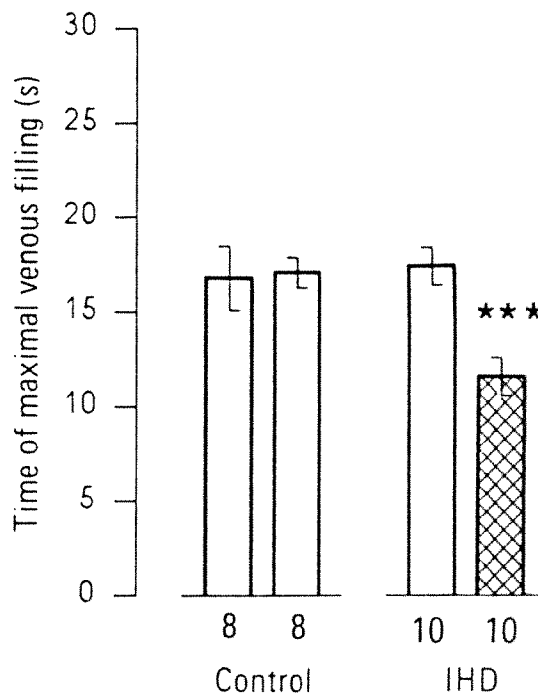


Fig. 3 Time of maximal venous filling (mean $\pm$ SEM) in eyes with non-ischaemic CRVO before and after isovolaemic haemodilution (hatched bars). Control patients (empty bars) received no treatment between the two angiograms. Number of eyes are given below the bars. $p < 0.005$ (***).

indicator of the efficiency of IHD, especially if one takes into account the ability to read ($\geq 6/15$). After three months the number of eyes with a visual acuity of 6/15 or better had fallen from eight to six in control patients and increased from seven to 10 in haemodiluted patients. One year later only four eyes of the control group compared with nine of the haemodilution group reached a visual acuity of 6/15 or more.

Only in 18 of 25 patients was it possible to get a series of two evaluable angiograms before and after IHD that could be compared with those of control patients without any treatment. The time of maximal venous filling (t_{mvt}) is an important parameter for the severity of CRVO¹⁴ and may be used as an indicator for blood velocity in retinal veins. It normally takes 5–12 s from the first arterial appearance of the dye on the papilla until complete or maximal filling of the veins.¹⁷ This arteriovenous passage time was prolonged to 16.8 (SEM 1.7) s ($n=8$) and 17.4 (SEM 1.4) s ($n=10$) in patients with non-ischaemic (CRVO) (Fig. 3). Two weeks later no change had occurred in control eyes (17.1 (SEM 0.8) s, $n=8$), whereas the t_{mvt} was reduced to 11.4 (SEM 0.9) s ($n=10$) in haemodiluted patients ($p < 0.0005$).

Discussion

The beneficial effect of isovolaemic haemodilution on the visual prognosis of patients with CRVO has been demonstrated before in two controlled studies.^{6,18} The shortcomings of these studies were as follows: (1) the results were mainly based on subjective findings like visual acuity; (2) though both studies paid regard to the type of CRVO, the question whether IHD might also be a useful procedure in non-ischaemic CRVO was not solved. Our first controlled trial of IHD in CRVO showed an effect more often in ischaemic than in non-ischaemic CRVO.

We did not change our treatment scheme,⁶ originally proposed by Wiederholt *et al.*¹⁹ Problems of method and the applicability of IHD in the clinical routine are discussed in a separate paper.²⁰

One rationale for IHD is the finding of Ring *et al.*² and McGrath *et al.*²¹ that patients with CRVO have higher whole blood and plasma viscosity than normal. These results have been corroborated^{9,21} for patients with ischaemic CRVO. In our measurements of different haemorheological parameters we did not find rheological abnormalities in patients with ischaemic and non-ischaemic CRVO, but, as has been shown also by Heinen *et al.*,²² the fluidity of whole blood was markedly increased after IHD.²³

Irrespective of a normal blood fluidity in patients with CRVO, local rheological factors should play a part in the compromised microcirculation of the retina. Independently of the primary event the blood flow decreases in venules and capillaries, thus leading to lower shear rates. It is well known that blood viscosity increases logarithmically with linear increase of PCV at a decrease of the shear rate. The increase of blood viscosity may be enhanced by haemoconcentration (plasma extravasation) and greater rigidity of erythrocytes (local acidosis). Thus a low blood velocity may strengthen a vicious circle and ultimately produce capillary lesions from ischaemia. To answer the question whether local rheological disturbances can be influenced by IHD we measured the time for maximal venous filling (t_{mvf}), which reflects the blood velocity in retinal vessels. A decrease of whole blood viscosity shortened t_{mvf} . In control patients with non-ischaemic CRVO no change of the passage time could be detected after two weeks. These findings suggest that the shortened t_{mvf} is induced by a lower whole blood viscosity and hence demonstrates the local efficacy of IHD.

The visual prognosis of CRVO depends very much on the type of occlusion.^{3,4,6,10,11,23} Randomised studies^{6,18} on IHD have shown that an increase in visual acuity is more often seen in haemodiluted than in non-haemodiluted patients. This holds true also

for patients with non-ischaemic CRVO, as has been shown by our randomised controlled trial (Figs. 1,2). If one considers all our haemodiluted patients,²⁰ improvements are more often seen in eyes with ischaemic CRVO. Nevertheless, the prognosis of non-ischaemic CRVO is still better than that of its ischaemic counterpart. An important measure of a patient's visual acuity is the ability to read. In non-ischaemic CRVO without haemodilution the rate of patients having a visual acuity of 6/15 or better fell, indicating that this disease is not as benign as has been claimed by Hayreh.²⁴ This fall could finally be prevented by IHD in most cases.

In conclusion this study has shown that IHD may improve the visual prognosis in non-ischaemic as well as in ischaemic CRVO. The improvement is probably induced by a decrease in whole blood viscosity, which leads to a higher blood velocity in areas of compromised retinal microcirculation. The effect of isovolaemic haemodilution only partly influences the visual prognosis of CRVO because it does not eliminate the cause of the obstruction.

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Fundus changes in mesangiocapillary glomerulonephritis type II: clinical and fluorescein angiographic findings

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SUMMARY Previously we have demonstrated a deposit in Bruch's membrane in a single case of mesangiocapillary glomerulonephritis type II. We studied a group of patients with this disease and described extensive clinical and fluorescein angiographic abnormalities, which were in marked contrast to the findings in a group of patients with other forms of glomerulonephritis. This finding contributes to our understanding of the pathophysiology of the complex of the retinal pigment epithelium, Bruch's membrane, and choriocapillaris.

A comparison can be made between the anatomy of the glomerulus and the choriocapillaris-Bruch's membrane-retinal pigment epithelium complex, in which the choriocapillaris is likened to the glomerular tuft, Bruch's membrane to the glomerular basement membrane, and the retinal pigment epithelium to the glomerular epithelium.¹

In a previous case report of a patient with type II mesangiocapillary glomerulonephritis (MCGN) we have demonstrated the occurrence of deposits in the choriocapillaris and Bruch's membrane which have the clinical appearance of drusen but the histopathological characteristics of deposits in the glomerulus.² In type II MCGN, which is frequently associated with partial lipodystrophy (PLD), deposits of electron dense material, often with a ribbon like appearance, are found within the glomerular basement membrane.³ This is in contrast to the discrete deposits found in (a) membranous nephropathy, where the material lies initially between the basement membrane and the epithelium; (b) in type I MCGN, where the deposit is predominantly sub-endothelial between the basement membrane and the endothelium; and (c) in mesangial proliferative glomerulonephritis, where the majority of the deposits are in the mesangium⁴ (Fig. 1).

We have therefore examined clinically the eyes of

patients with a variety of glomerular disorders, including further cases of type II MCGN and partial lipodystrophy (PLD), and report our findings.

Methods and patients

From the diagnostic index at the Manchester Royal Infirmary Renal Unit we selected for ophthalmic investigation 17 patients with biopsy proved glomerular disease and two further patients with PLD but who had never had a renal biopsy. The histological diagnosis was withheld from the ophthalmologists who examined the patients by routine clinical methods, fundus photography, and fundus fluorescein angiography. All the patients were normotensive and had been so for some months, though many had had a period of hypertension earlier in the course of their illness. Patients 4, 7, and 13 had reached end stage renal failure and had had successful renal transplantation at the time of the study. No patient was receiving dialysis.

Details of the patients are given in Tables 1, 2, and 3.

Results

None of the patients had ocular symptoms. All the anterior segments appeared normal and no hypertensive retinopathy was detected.

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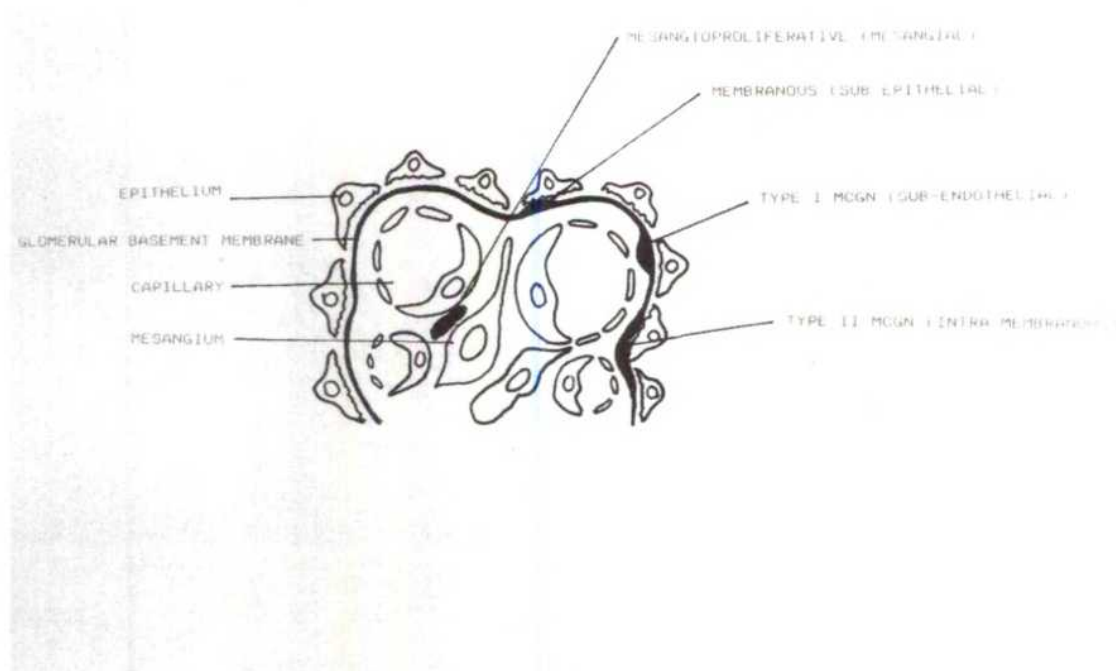


Fig. 1 Predominant sites of deposition of immunoreactive and electron-dense material in various glomerulopathies.

Of the 12 patients without PLD six had type I MCGN, one had minimal change disease (a term used by renal pathologists to describe a nephritis in which there is no evidence of disease on light microscopy), and five had membranous nephropathy.

Table 1 Clinical details of cases with PLD

Case	Age (yr)	Sex	Glomerular disease	Time since diagnosis (yr)	Blood pressure (mm Hg)	Current medication
1	43	M	MCGN II	0.6	140/90	Tenoretic Nifedipine Hydralazine
2	45	F	MCGN (type unknown)	27	135/90	Atenolol Methyldopa Bendroflumazide
3	28	F	MCGN II	24	130/80	Cyclosporin Atenolol
4	36	M	MCGN II	2.2	150/85	Allopurinol Captopril Frusemide
5	30	F	Nephrotic syndrome; no biopsy	14	150/80	Cyclosporin Prednisolone Atenolol
6	43	F	No biopsy; normal renal function		110/70	Anxiolytics
7	43	M	MCGN II	31	115/70	Tenoretic

Tenoretic=atenolol 100 mg and chlorthalidone 25 mg.

Ophthalmoscopic examination of these eyes revealed a few drusen (Fig. 2), but with no difference in

Table 2 Clinical details of cases without PLD

Case	Age (yr)	Sex	Glomerular disease	Time since diagnosis (yr)	Blood pressure (mm Hg)	Current medication
8	51	M	Membranous	2	180/100	Prednisolone Atenolol Nifedipine
9	31	M	MCGN I	6	140/90	Nil
10	43	F	MCGN I	9	140/85	Nil
11	44	F	MCGN I	6	160/90	Azathioprine Prednisolone Atenolol
12	73	M	Membranous	5	140/70	Nil
13	49	F	MCGN I	1	180/95	Prednisolone Azathioprine Atenolol Nifedipine
14	39	M	Membranous	6	125/90	Bendroflumazide
15	32	M	Membranous	2	140/90	Prednisolone Frusemide Spironolactone
16	25	F	MCGN I	1.5	150/90	Nil
17	50	M	MCGN I	13	160/90	Methyldopa Frusemide Propranolol
18	29	F	Minimal change	3	90/60	Nil
19	50	F	Membranous	7	130/80	Nil

Table 3 Summary of patients

With partial lipodystrophy		Without partial lipodystrophy	
Type II MCGN	4	Type I MCGN	6
MCGN unclassified	1	Minimal change	1
End stage renal failure	1	Membranous	5
No renal lesion	1		
Total	7		12

frequency from that expected in normal age matched population. Similarly the fluorescein angiograms showed only a few hyperfluorescent spots corresponding to scattered drusen.

Of the seven patients with PLD (Table 4) five were found to have a very striking abnormality in the fundi (Figs. 3,4,5). There was a regular, bilaterally symmetrical distribution of discrete yellow spots, similar to drusen, more densely present posteriorly but spreading up to and beyond the equator. The lesions were not elevated, but were associated with some 'irregularity' of pigmentation. In the same five patients fluorescein angiography showed gross abnormalities correlating with the drusen-like appearance, and similar to that seen in the previous case report,² with hyperfluorescence corresponding to the yellow lesions but with no leakage of fluorescein. There was some variation from case to case in the dimensions and distribution of the deposits, but there was symmetry within each case. The visual acuity was unaffected. Four of these five cases had biopsy proved type II MCGN, and the fifth was likely to be in this category on the basis of PLD and nephrotic syndrome, though no biopsy was ever taken.

Two patients with PLD had normal ophthalmoscopic and angiographic appearances. One had unclassified MCGN, and the other had no evidence of glomerular disease.

Table 4 Ophthalmic findings in cases with PLD

Case	Visual acuity		Fundus examination	Fluorescein angiography
	R	L		
1	6/6	6/9	Massive drusen-like deposits and mottled pigmentation	Extensive hyperfluorescence in Bruch's membrane
2	6/6	6/5	Drusen-like deposits and mottled pigmentation	Few corresponding hyperfluorescent spots over drusen
3	6/6	6/6	Massive drusen-like deposits and mottled pigmentation	Extensive hyperfluorescence
4	6/9	6/9	Massive drusen-like deposits and mottled pigmentation	Extensive hyperfluorescence
5	6/36	6/24	Massive drusen-like deposits and mottled pigmentation	Extensive hyperfluorescence
6	6/6	6/6	Normal	Normal
7	6/5	6/5	Massive drusen-like deposits and mottled pigmentation	Extensive hyperfluorescence in Bruch's membrane

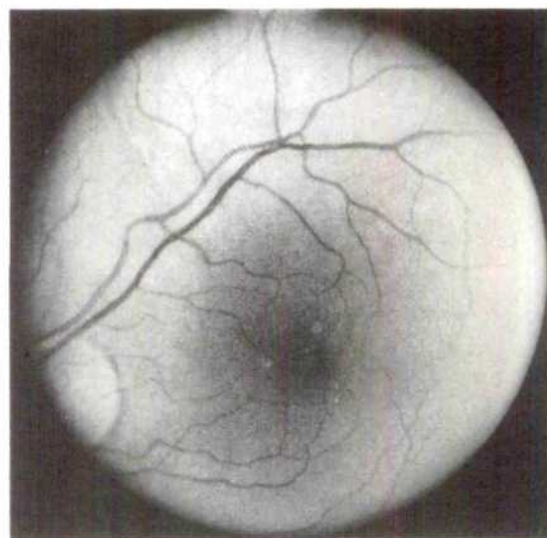


Fig. 2 Fundus photograph of case 18 showing scattered drusen at the posterior pole.

Discussion

We have described for the first time, to our knowledge, in this and in our recent publication² an abnormal deposit in the eye at the level of Bruch's membrane and choriocapillaries in type II mesangio-capillary glomerulonephritis. Our findings in this communication support the hypothesis that the choriocapillaris - Bruch's membrane - retinal pigment epithelial complex may respond to disease in a similar way to the glomerulus.

The previously reported fundus changes seen in glomerular disease can be broadly divided into those associated with hypertension, those associated with vasculitis causing glomerulonephritis, those resulting from treatment of the renal lesion, and those

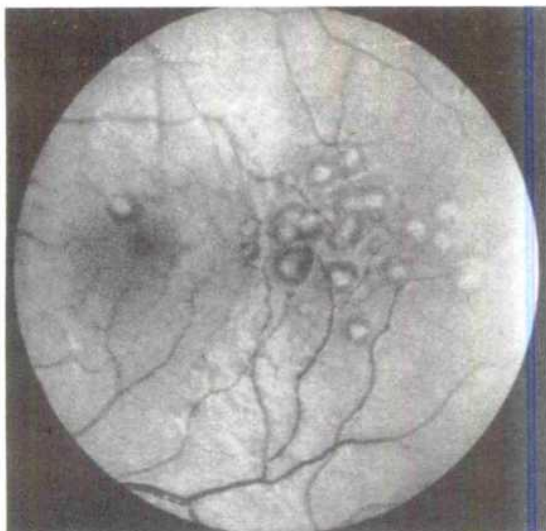


Fig. 3A

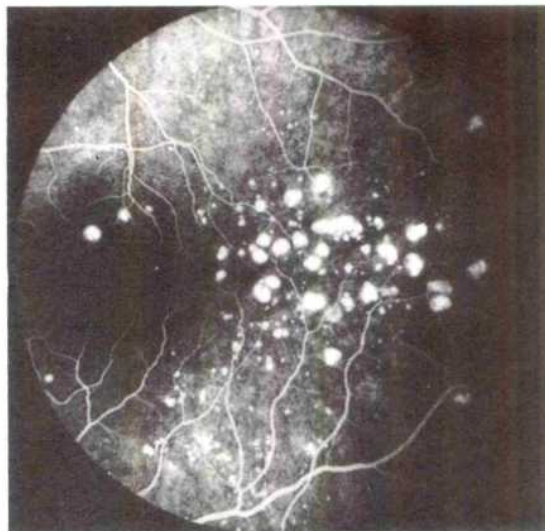


Fig. 3B

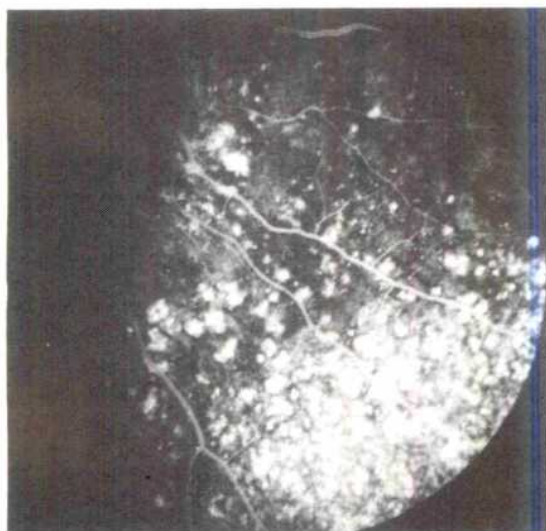


Fig. 3C

Fig. 3 A: Fundus photograph and B, C, fluorescein angiogram of case 4 showing large posterior pole deposits with a pigmented halo temporal to the macula, associated with intense focal hyperfluorescence which extends towards the equator.

considered to be specifically related to the renal lesion.⁵ In systemic hypertension the fundus abnormalities are well recognised, and they are described in renal patients. In accelerated hypertension infarcts of the retinal pigment epithelium, corresponding to failure of lobules of choriocapillaris to be perfused, termed Elschnig's spots, are described,⁶ but they

differ from the lesions we report in that they are much more widespread and are not associated with the focal pigment clumping seen in Elschnig's spots. In addition there is no history of visual disturbance in any of our patients, whereas if there were such widespread infarction of the retinal pigment epithelium visual symptoms would be expected.

A series of patients with glomerulonephritis with and without hypertension have been studied ophthalmoscopically. None of these showed any fluorescein angiographic abnormality, though the type of glomerulonephritis was not identified.

Vasculitis, such as is seen in systemic lupus erythematosus, may involve the renal circulation as well as the retinal and choroidal circulation, giving rise to cotton-wool spots, haemorrhages, swelling of the optic nerve head, and vascular occlusion.^{7,17} In the cases we have studied no features of vasculitis were present.

Ocular complications of chronic renal disease involve exudative retinal detachment¹³ and crystals of cystine in the cornea and retina,¹⁴ and the complications of treatment include cataract, raised intraocular pressure, opportunistic retinitis,¹⁵ and retinal microaneurysms.¹⁶

A number of familial disorders are described which affect the eye and kidney. Those which involve the retina and choroid include Alstrom's syndrome,¹⁷⁻²⁰ which comprises pigmentary retinopathy, obesity, diabetes mellitus, and nerve deafness, often associated with renal insufficiency; Alport's syndrome,²¹⁻²³ which is characterised by lenticonus, spherophakia, sensorineural deafness, and a hereditary nephropathy and sometimes pigmentary

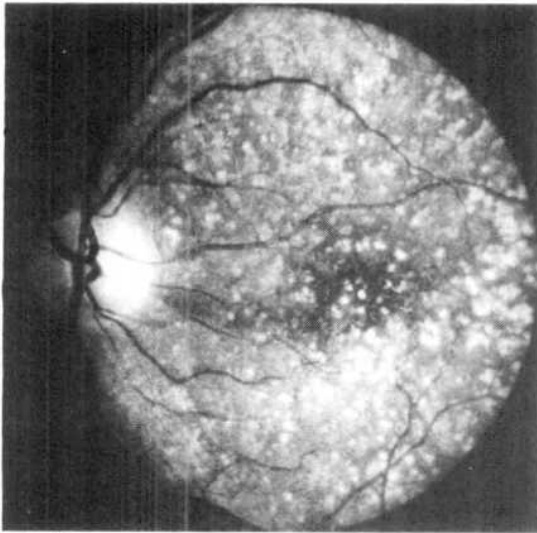


Fig. 4A

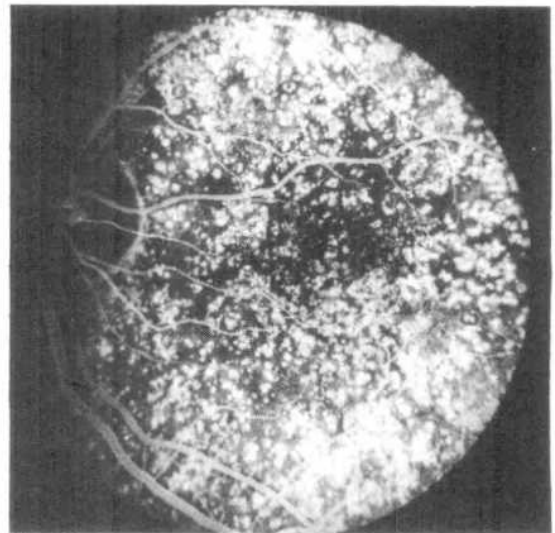


Fig. 4B

Fig. 4 A: Fundus photograph and B, fluorescein angiogram of case 10 showing scattered drusen-like deposits with intense hyperfluorescence.

retinopathy with or without subretinal and Bruch's membrane deposits; and adult polycystic kidney disease.²⁴ A miscellaneous group of hereditary renal lesions associated with other fundus abnormalities, usually manifest as pigmentary retinopathies, are described.²⁵⁻²⁹ The only previous publications comparing pathology of the kidney and eye refer to

patients with diabetes mellitus: microaneurysms have been described in the glomerulus³⁰ and lesions resembling Kimmelsteil-Wilson nodules were described in the choroid.³¹

Bruch's membrane and the glomerular membrane are structurally homologous in that both are selectively and directionally permeable,³²⁻³⁴ with a positive

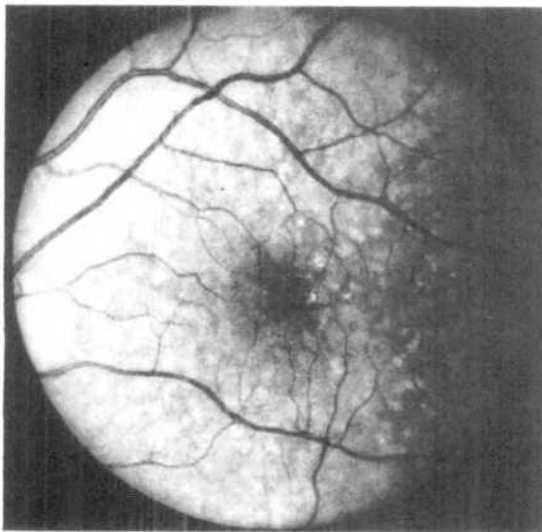


Fig. 5A

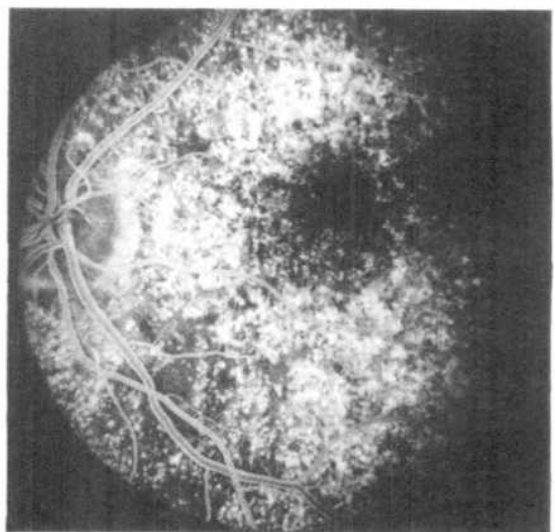


Fig. 5B

Fig. 5 A: Fundus photograph and B, fluorescein angiogram of case 19 showing extensive drusen-like deposits with hyperfluorescence.

charge and a high heparan sulphate content.^{32,36} The two membranes differ in that the collagenous zones of Bruch's membrane make it much thicker than the glomerular basement membrane. Pathological changes in the renal glomerular basement membrane with similarities to those seen in Bruch's membrane are identifiable. In aging, the glomerular basement membrane is focally thickened, with the appearance of vesicles in the membrane³⁷ similar to the aging changes of Bruch's membrane.³⁸ In aminoglycoside nephrosis, deposits with an ultrastructural similarity to drusen are present on the epithelial side of the glomerular basement membrane.³⁹ Aminoglycoside toxicity has been used as an experimental means of creating drusen in the eye.⁴⁰ Breaks in the glomerular basement membrane, reminiscent of angiod streaks in Bruch's membrane, have also been described.⁴¹

The nature of deposits in different types of glomerulonephritis differs histologically and presumably also pathogenetically. We suggest that, whatever the pathogenesis in MCGN type II, a similar setting pertains in Bruch's membrane, whereas in the other forms of glomerulonephritis this may not be the case. Recently an early case of MCGN II has been studied histopathologically.⁴² It is interesting that the early lesion prior to the appearance of the dense deposit is lamellation of the lamina densa of the glomerular basement membranes, very reminiscent of the appearance seen in Alport's syndrome,⁴³ which is undisputably associated with a chorioretinal lesion.^{44,45}

Our findings suggest that, in patients with type II MCGN and PLD, chorioretinal changes similarly may parallel those found in the kidney. Although in all five patients with PLD and fundus changes the ophthalmic findings were very similar, the duration of renal disease ranged from 7 months to 31 years, and sequential observation is necessary to determine whether a lesion is static or variable with time. There is undoubtedly a structural and a pathological comparison to be drawn between the eye and the kidney, and further investigation of patients with glomerular disease may well shed light on the pathophysiological responses of the complex of choriocapillaris, Bruch's membrane, and retinal pigment epithelial. Similarly, study of the ocular responses may contribute to the understanding of the pathogenesis of the renal lesion.

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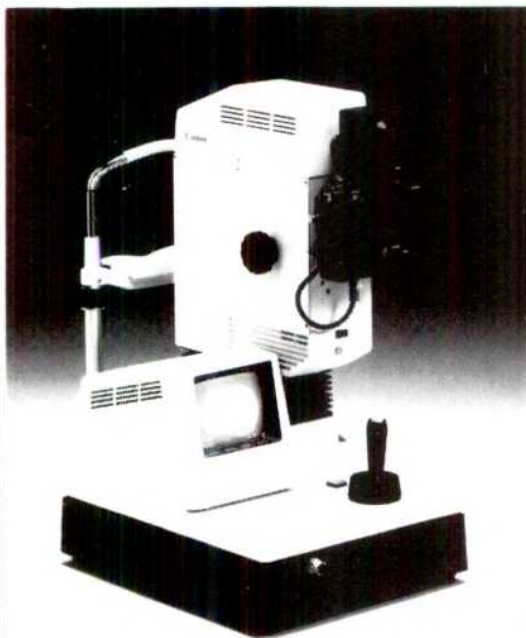
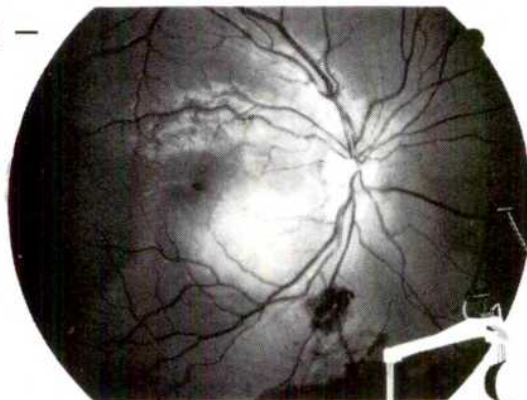
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Fundus changes in mesangiocapillary glomerulonephritis type II: vitreous fluorophotometry

M F RAINES,¹ J DUVALL-YOUNG,² AND C D SHORT³

From the ¹Manchester Royal Eye Hospital, ²Department of Ophthalmology, University of Manchester, and ³Department of Renal Medicine, University of Manchester

SUMMARY We have described a complex abnormality of retinal pigment epithelium, Bruch's membrane, and choriocapillaris in mesangiocapillary glomerulonephritis (MCGN) type II. Patients with MCGN type II were examined by vitreous fluorophotometry which reveals that there is a breakdown of the blood retinal barrier (BRB) in those patients with the typical fundus lesions. The function of this barrier was calculated as a penetration ratio and was statistically greater in these patients when compared with a group of (a) normal persons, (b) patients with drusen, and (c) patients with other forms of glomerulonephritis.

We have described marked changes in the complex of retinal pigment epithelium, Bruch's membrane, and choriocapillaris in patients with mesangiocapillary glomerulonephritis (MCGN) type II, by histopathological examination¹ and by clinical examination, including fluorescein angiography.² The characteristic abnormality clinically has the appearance of widespread drusen but histopathologically was shown to be a deposit in the choriocapillaris and Bruch's membrane, similar to the diagnostically electron dense deposit seen in the renal glomerulus by ultrastructural examination.

We examined a group of patients with MCGN type II by vitreous fluorophotometry and compared them with a group of normal persons, a group of patients with other forms of glomerulonephritis, and a group of patients with degenerative drusen.

Patients and methods

Of the group of patients previously studied² with glomerulonephritis and/or partial lipodystrophy (PLD), 15 were also examined by vitreous fluorophotometry. Thirteen of these patients had biopsy proved renal disease: four had MCGN type II, four had MCGN type I, and five had membranous glomerulonephritis. A further two patients had PLD, which is frequently associated with MCGN type II.³ One of these latter patients had no evidence of

glomerular disease despite many years of observation, with normal serum creatinine values and no proteinuria. The other had reached end stage renal failure, no biopsy was available but the presumed diagnosis was MCGN type II.

The classification of the renal lesion was withheld from the ophthalmologists who examined the patients by routine clinical methods.

All patients undergoing vitreous fluorophotometry were normotensive at the time of examination and had been for several months with or without treatment. None were diabetic, a condition known to affect the fluorophotometric readings. Careful indirect ophthalmoscopy and slit-lamp biomicroscopy excluded other conditions such as posterior vitreous detachment, which may also affect the readings.

With written consent vitreous fluorophotometry was performed with the Fluorotron Master (Coherent, Palo Alto, California) by standard recognised techniques.^{4,5} Both eyes were dilated with tropicamide 1% and phenylephrine 10% to attain maximum dilatation and cycloplegia. A baseline background scan was performed on each eye to assess the natural fluorescence of the eye. Sodium fluorescein was injected intravenously at the antecubital fossa in a dose of 14 mg/kg body weight. Standard fluorescein angiography was then performed. Between 3 and 5 minutes after injection a further scan, termed the bolus scan, was recorded on each eye to account for any chorioretinal spread function that may occur. This spread function is a

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result of fluorescein in the choroid-retina influencing the readings taken in the vitreous. The bolus scan may be used in the final calculations to minimise this influence. A final measurement scan was read at 60 minutes after injection.

Venous blood, 10 ml, was drawn from the opposite arm to the fluorescein injection, between 5 and 10 minutes after injection, and also at the end of the examination. Exact times of scans and venepuncture after fluorescein injection were recorded. Plasma fluorescence was measured by means of the special cuvettes and the plasma adapter supplied with the Fluorotron. The plasma values were incorporated into a recognised computer algorithm to attain the fluorescein plasma integral.

For analysis we used the ARVO 85 (Coherent) program. The preinjection scan was subtracted from the measurement scan as only low levels of fluorescein leakage were identified. This manoeuvre minimises the contribution of natural fluorescence, which comes predominantly from the lens. The average value of fluorescence at a distance between 2 mm and 4 mm anterior to the retina was recorded. This has been shown to be relatively free of interference from the chorioretinal spread function.³ A final posterior vitreous penetration ratio (PR) for the eye was obtained from this finding.⁴

Some patients were examined on more than one occasion, in which case the penetration ratios of the different recordings were averaged. Results from these patients were then compared with penetration ratios obtained from a group of normal individuals (49 eyes from 35 patients) and also from a group of patients with clinically and fluorescein angiographically proved drusen (11 eyes from 11 patients).

Results

The four patients with MCGN type II had clinical and fluorescein angiographically demonstrable deposits in the fundus in both eyes.² The one patient with PLD, end stage renal failure, and presumed MCGN type II had penetration ratios (average PR=1.514) within the normal range despite having clinical and fluorescein angiographically proved deposits in the fundus. The other patient with PLD but without detectable renal disease had abnormally high penetration ratios (PR=3.41) despite having a clinically normal fundus. The mean penetration ratio values are shown in Table 1.

Normal methods of analysis rely on observations being independent, which they are patently not if measurements are performed on both eyes of the same individual. The method of Rosner,⁵ which adjusts for this lack of independence, was employed by means of the GLIM statistical package.⁶ This

showed that age had an insignificant negative effect on the values ($p=0.116$). With this small effect controlled for and the correlation between eyes taken into account, the findings were that the PRs in patients with MCGN type II were significantly greater than those of all other patients ($p=0.018$). The PRs of the patients with drusen were not significantly different from those of the normal control patients. The PRs of the remaining renal patients were lower than those of the normal controls ($p=0.033$).

All patients had plasma albumin concentrations within normal limits. There was no significant difference between the plasma albumin levels in type II MCGN and the remaining types of glomerulonephritis. Similarly, there was no significant difference in the 24-hour urinary protein in these two groups.

Discussion

We have previously noted that a comparison between the anatomy of the glomerulus and the complex of the choriocapillaris, Bruch's membrane, and retinal pigment epithelium can be made and have documented the ocular changes found in mesangio-capillary glomerulonephritis (MCGN) type II – that is, deposits in the choriocapillaris and Bruch's membrane, having similar histopathological characteristics to those in the glomerulus, but with the clinical appearance of drusen.^{1,2} Our findings with vitreous fluorophotometry show that there is breakdown of the blood retinal barrier in patients with MCGN type II. All our patients were unaware of any ocular lesion.

Vitreous fluorophotometry has been shown to be a sensitive and quantifiable method of assessing the blood retinal barrier,^{9,10} which is found at the tight junctions of the retinal pigment epithelial cells and the endothelial cells of the retinal capillaries.^{11,12}

Vitreous fluorophotometry has been recorded in many ocular conditions, including diabetic^{6,9,10,13,16} and hypertensive^{17,19} retinopathies, pars planitis,²⁰ and retinitis pigmentosa.^{21–25} In these conditions the BRB breaks down, as shown by increased leakage of fluorescein into the vitreous. The degree of

Table 1 Posterior vitreous penetration ratios

Type	No of patients	No of eyes	Mean penetration ratios $\times 10^{-4}/\text{minute}$ (SD)
MCGN II	5	10	3.099 (0.946)
Drusen	11	11	2.280 (0.615)
Normals	35	49	2.313 (0.676)
Other renal patients	10	20	1.818 (0.762)

fluorescence detected in the vitreous is related to the extent of chorioretinal disease, such that increased penetration ratios are found with increased severity of, for example, diabetic retinopathy. If we postulate that the deposits found in the eyes of patients with MCGN type II are similar to drusen, then the overlying pigment epithelium may atrophy with time, as is seen with drusen.²⁶ With this atrophy there may exist breakdown of the BRB, which may explain the findings in our patients.

One of our patients with PLD had been followed for many years without evidence of renal impairment: her serum creatinine had always been normal and there was no proteinuria. However, her vitreous fluorophotometry readings and penetration ratios were abnormally high (PR=3.41) and were reproducible on different occasions. Fluorescein angiography gave normal results. We are unable to explain this high reading, though it may represent a sub-clinical phenomenon, as it is known that some patients with PLD have a histological renal lesion which is clinically undetectable.²⁷ Likewise this patient may have had ocular disease which was undetectable by conventional methods of examination, including fluorescein angiography. We also found vitreous fluorophotometric readings within normal limits in one patient who did have clinical and fluorescein angiographically proved chorioretinal deposits (PR=1.514). The lesions seen, however, were not as florid as those of the other renal patients and in particular were not extensive at the macula (Fig. 1).

None of our patients had other detectable ocular lesions. Systemic hypertension can affect the fluorophotometry readings,¹⁷⁻¹⁹ but none of our patients had signs of hypertensive retinopathy.

Our group of patients with drusen did not show penetration ratios of the same magnitude as our patients with MCGN type II. This can be explained by the fact that the drusen observed (Fig. 2) were not as widespread as the deposits found in the patients with MCGN type II (Fig. 3). In a recent report of a group of patients with drusen fluorophotometric readings were found to be within normal limits, but the extent of the drusen was not specified.²⁸ Owing to the widespread nature of the deposit we describe, it cannot be compared directly with drusen. The findings, however, indicate that deposits in Bruch's membrane cause retinal pigment epithelial dysfunction. This has never been previously demonstrated. That the dysfunction is present at the cellular level or at the cell junctions themselves is impossible to differentiate.

We propose that there is retinal pigment epithelial dysfunction in MCGN type II as shown by the breakdown of the blood retinal barrier, and this is

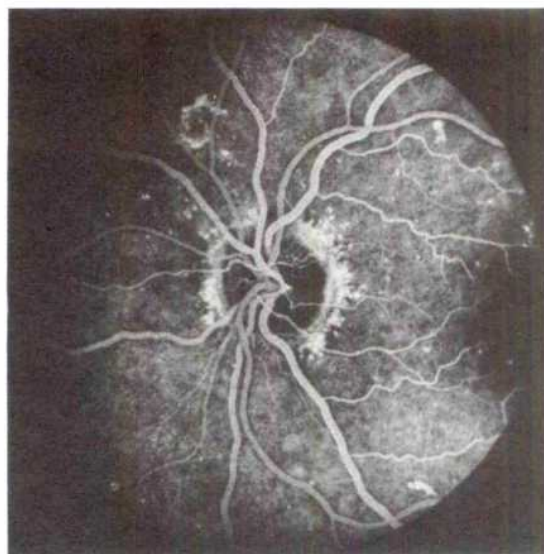


Fig. 1 Fluorescein angiogram of patient with MCGN II showing minimal chorioretinal deposits particularly at the macula, and normal penetration ratios.

likely to be a result of the deposits interfering with the retinal pigment epithelial layer.

The fluorophotometric findings in diabetics without retinopathy are controversial,^{6,9,10,13-16} but if an abnormality does exist our findings support the possibility of an asymptomatic retinal pigment epithelial dysfunction. Because of the similarity

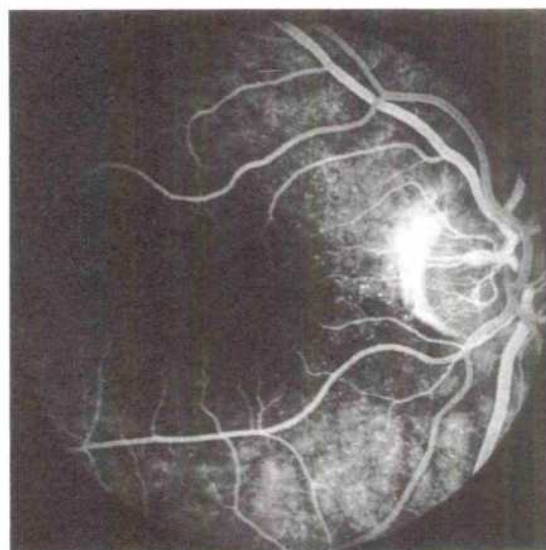


Fig. 2 Fluorescein angiogram showing extent of typical patient with drusen.

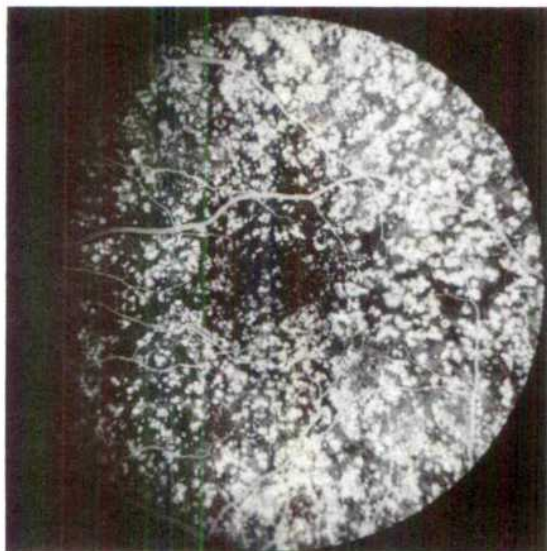


Fig. 3 Fluorescein angiogram showing typical extent of chorioretinal deposits at the macula in patient with MCGN II and raised penetration ratios.

between the anatomy of the glomerulus and the complex of choriocapillaris, Bruch's membrane and retinal pigment epithelium it would be helpful to explore eye and renal function in parallel in other disease processes.

We are grateful for advice from Mr David Shaw, medical statistician, University of Birmingham Medical School.

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Clinical parameters predictive of enlargement of melanocytic choroidal lesions*

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SUMMARY The authors followed up 197 melanotic choroidal lesions (62 categorised as benign naevi, 76 classified as suspicious naevi, 41 diagnosed as dormant melanomas, and 18 categorised as active melanomas) left untreated after their initial clinical documentation. Thirty-nine of these lesions enlarged during a five-year follow-up interval (cumulative proportion of lesions that enlarged=26.2% by Kaplan-Meier method). Individual clinical parameters predictive of lesion enlargement ($p<0.01$) included larger size of the lesion, especially lesion thickness, presence of retinal detachment, location of the lesion's posterior margin within 2 disc diameters of the optic disc, presence of symptoms, and presence of orange pigment clumps on the lesion's surface. The best combination of these parameters for prediction of lesion enlargement, as identified by multivariate Cox regression analysis, consisted of thickness of the lesion, retinal detachment, and symptoms. The five-year incidence of lesion enlargement for patients with none of these prognostic parameters was 5.8%, while that for patients with all three unfavourable parameters simultaneously was 90.6%.

In spite of improvements in ophthalmic diagnostic methods, clinical differentiation between benign choroidal naevi and malignant melanomas is not completely reliable.^{1,2} Clinical parameters currently used to assist in this distinction include lesion size, symptoms, presence or absence of orange pigment and drusen on the surface of the lesion, extent of serous retinal detachment, and lesion enlargement.¹⁻⁹ Of these parameters, enlargement of the lesion is generally regarded as the most reliable predictor of malignant potential in a melanocytic choroidal lesion.^{6,8}

Growth of a choroidal lesion initially diagnosed as a benign naevus usually prompts reclassification of the lesion as a melanoma and consideration of

treatment.^{1,6} However, a number of studies have shown that only a small proportion of clinically diagnosed choroidal naevi and small melanomas enlarge during short-term follow up.^{6,8,9} Surprisingly, little is known about which clinical parameters predict lesion enlargement. To study this question the authors investigated the ability of various clinical parameters assessed at initial diagnostic examination to predict enlargement of melanocytic choroidal lesions.

Patients and methods

The authors surveyed the clinical records of all new patients examined at the Oncology Service of Wills Eye Hospital between 1 July 1980 and 30 June 1982, with the aid of a computerised patient database. The records of all patients diagnosed on initial examination as having a choroidal lesion classified as a freckle, non-suspicious naevus, suspicious naevus, dormant melanoma, or active melanoma (as defined by Shields¹⁰) were reviewed. Those records indicating that the patient had been managed, at least initially,

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by observation without treatment were selected for data abstraction.

Clinical parameters extracted from the written clinical records of these patients included age at presentation, sex and race, presence or absence of symptoms attributable to the tumour, duration of any symptoms attributable to the lesion, and best corrected distance visual acuity (Snellen notation). Chart notations, fundus diagrams, and fundus photographs were used to assess colour of the lesion, lesion basal diameters (estimated to the nearest 0.5 mm) and thickness (measured by standardised A-scan ultrasonography), location of the anterior margin of the lesion in relation to the equator, location of the posterior margin of the lesion relative to the optic disc and foveola, and presence and extent or absence of serous non-rhegmatogenous retinal detachment. The presence or absence of orange pigment clumps, drusen, and black retinal pigment epithelial pigment clumps on the surface of the lesion were assessed on the fundus photographs of each lesion relative to a set of standard fundus photographs (Figs. 1–3). If the extent of any of these features was as great as or greater than the extent of the features depicted in the standard photographs, the feature was coded present.

The result of interest in this study was recorded enlargement of the lesion verified by fundus photography, ultrasonography, or both. For each patient whose melanocytic choroidal lesion enlarged during follow-up the duration of follow-up was computed as the interval between the patient's initial diagnostic examination and the date when enlargement of the lesion was recorded. In contrast, for patients whose lesion did not enlarge during observation the duration of follow-up was computed as the interval between the initial examination and the patient's most recent follow-up visit.

Conventional descriptive statistics were used to summarise the recorded parameters in these patients. The cumulative proportion of the melanocytic choroidal lesions which enlarged during follow-up was computed by the method of Kaplan and Meier.¹¹ Patients with lesions that enlarged were compared by unpaired *t* testing and χ^2 analysis with patients with lesions that did not.

Cox proportional hazards modelling¹² was used to assess the prognostic value of the recorded clinical parameters for prediction of subsequent lesion enlargement. Both univariate and multivariate regressions were explored. For the multivariate analysis a special algorithm written by one of us (JWG) was used to test all possible two-term and three-term Cox regressions. A multivariate regression was considered to be significant only if all component variables entered at a statistically signi-

ficant level. Because of the exploratory nature of this study and the multiplicity of assessed variables the authors specified a conservative significance level of $\alpha=0.01$ in advance of data analysis. The best two-term and three-term models were determined from among the significant Cox models by the following method: (a) a prognostic index (hazard ratio) was computed for each case from the β coefficients estimated for the particular Cox model; (b) the cases were divided into low-risk and high-risk groups according to the mean hazard ratio predicted from the β coefficients computed from the Cox model; and (c) five-year Kaplan-Meier lesion non-enlargement rates for the two groups were computed for each of the significant models.

Results

The authors identified 197 lesions which fulfilled the inclusion criteria of this study. Our initial clinical diagnosis was freckle or benign naevus in 62 (31.5%), suspicious naevus in 76 (38.6%), dormant melanoma in 41 (20.8%), and active melanoma in 18 (9.1%). The affected patients ranged in age from 15 to 87 years (mean 58.1, SD 13.4 years). All of the patients were white. Seventy-nine of the lesions (40.1%) occurred in males and 118 (59.9%) in females. One hundred and one of the 197 lesions (51.3%) involved the right eye and 96 involved the left (48.7%). One hundred and forty-six of the 197 choroidal lesions were asymptomatic, but 51 of the lesions (25.9%) were associated with visual symptoms.

The lesions of interest ranged in size from 0.5 to 15.5 mm in basal diameter (mean 5.2, SD 3.1 mm) and from flat to 8.0 mm in thickness (mean 1.3, SD 1.3 mm). Pigmentation of the lesion was categorised as amelanotic in nine (4.6%), intermediate in 64 (32.5%), and darkly melanotic in 124 (62.9%). One hundred and forty-eight of the 179 lesions (75.1%) were located entirely posterior to the equator, while 49 (24.9%) either straddled the equator or were entirely pre-equatorial. The posterior margin of the lesion was over 2 disc diameters from the optic disc in 128 eyes (65.0%), within 2 disc diameters from the optic disc in 48 eyes (24.4%), and touching the optic disc margin in 21 eyes (10.6%). Nineteen of the 197 lesions (9.6%) involved the subfoveolar choroid; 44 additional lesions (22.3%) were located within 2 disc diameters of the foveola, and 134 lesions (68.0%) were more than 2 disc diameters from the foveola.

One hundred and sixty-one of the 197 choroidal lesions had no associated retinal detachment. Of the remaining lesions 26 (13.3%) were associated with a localised collection of subretinal fluid extending no more than 1 disc diameter beyond any margin of the

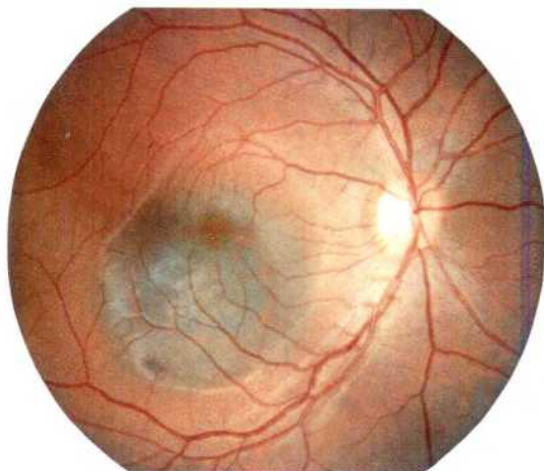


Fig. 1 Standard photograph used to identify orange pigment clumps on the surface of a melanocytic choroidal lesion.

lesion, and nine (4.6%) were associated with a more extensive non-rhegmatogenous retinal detachment.

Orange pigment clumps equal to or greater in extent than those depicted in our standard photograph (Fig. 1) were identified on the surface of 17 of the 197 choroidal lesions (8.6%). In contrast, drusen equal to or greater in extent than those shown in our standard photograph (Fig. 2) were present on 83 (42.1%) of the 197 lesions, and black retinal pigment epithelial pigment clumps equal to or greater in extent than those shown in our standard photograph (Fig. 3) were found on only 25 of the 197 lesions (12.7%).

Thirty-nine of the 197 lesions enlarged during the

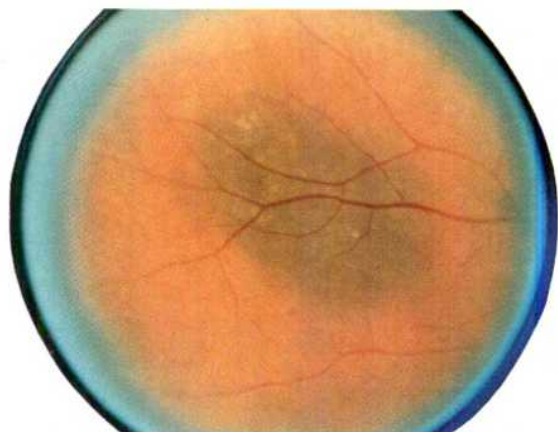


Fig. 2 Standard photograph used to identify drusen on the surface of a melanocytic choroidal lesion.



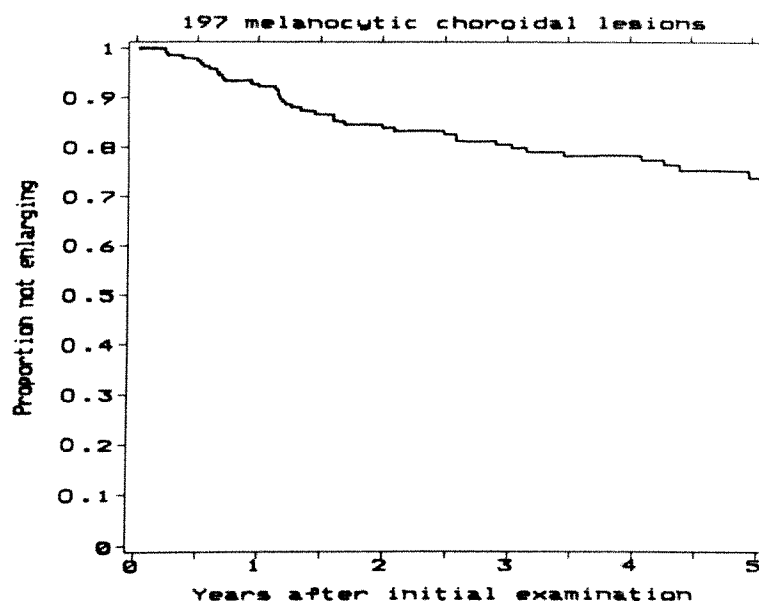
Fig. 3 Standard photograph used to identify retinal pigment epithelial pigment clumping on the surface of a melanocytic choroidal lesion.

interval of study. The Kaplan-Meier estimate of the cumulative proportion of lesions enlarging within five years was 26.2 (SE 4.8)% (Fig. 4). The proportion of lesions which did not enlarge as a function of our initial clinical diagnosis is presented graphically as Fig. 5. This figure indicates that only 4.5% of melanocytic choroidal lesions diagnosed clinically as 'benign naevi' enlarged during five years of follow-up. In contrast, 14.2% of lesions diagnosed as 'suspicious naevi', 50.1% of lesions categorised as 'dormant melanomas', and 86.1% of lesions classified as 'active melanomas' enlarged during the same period of follow up.

Table 1 compares the 39 lesions which enlarged with the 158 which remained unchanged in size with regard to the distribution of the assessed clinical variables. The lesions that grew were larger and located nearer the optic disc than those that remained stable. Furthermore, a higher proportion of lesions that enlarged had associated subretinal fluid, prominent orange pigment clumps on their surface, and related symptoms than did lesions that remained unchanged in size.

Table 2 presents the results of univariate prognostic factor analysis by Cox proportional hazards modelling. Larger size of the lesion (especially lesion thickness), more extensive retinal detachment, more posterior location of the lesion's posterior margin, presence of symptoms, and orange pigment clumps on the lesion's surface were all significant individual predictors ($p < 0.01$) of lesion enlargement.

Fig. 4 Kaplan-Meier estimate of the cumulative proportion of 197 melanocytic choroidal lesions which did not enlarge during five years of follow-up.



The best multivariate statistical model for predicting lesion enlargement was a three-term regression incorporating thickness of the lesion, extent of retinal detachment, and symptoms (logrank test $t=7.5$, $p<0.0001$). This model allowed us to divide the 197 cases into a low-risk group of 160 lesions with a five-year lesion enlargement rate of 10.9% and a high-risk group of 37 lesions with a five-year lesion

enlargement rate of 86.2%. The best alternative multivariate model not incorporating lesion thickness was a three-term regression incorporating the lesion's basal diameter, symptoms, and age of the patient. The best alternative regression not incorporating any lesion size parameter was a two-term regression including symptoms and orange pigment on the lesion's surface.

Fig. 5 Relationship between time to lesion enlargement and initial clinical diagnosis of 197 melanocytic choroidal lesions. Lesions were categorised as freckles and non-suspicious naevi (NN), suspicious naevi (SN), dormant melanomas (DM), or active melanomas (AM).

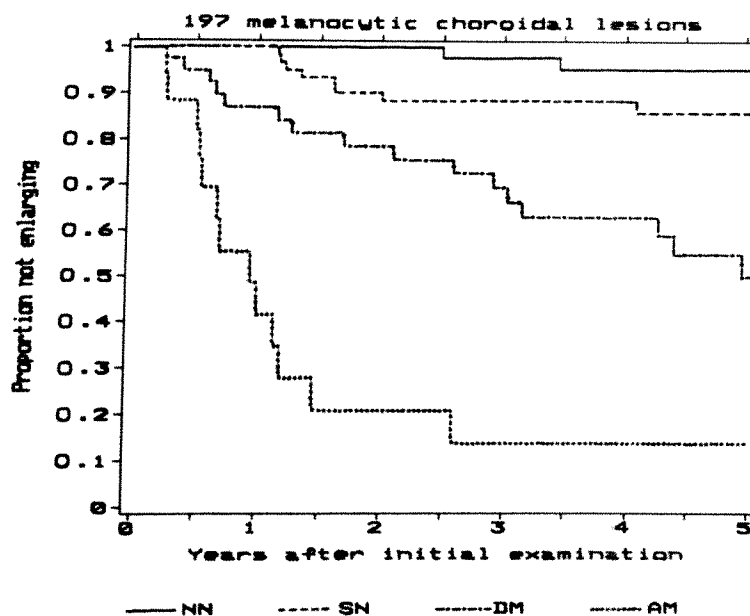


Table 1 Distribution of clinical variables by lesion enlargement category for 197 patients with a melanocytic choroidal lesion

Variable	Category	Lesion enlargement category		χ^2	df	p
		Enlarged (n=39)	Not enlarged (n=158)			
		No. of mean* cases	No. of mean* cases			
Age	<40 yr	7	9	10.0	4	0.040
	≥40 to <50 yr	5	20			
	≥50 to <60 yr	12	47			
	≥60 to <70 yr	7	59			
	≥70 yr	8	23			
Sex		54.4±17.9	59.1±11.9	t=1.97		0.049
	Male	16	63	0.003	1	0.96
Eye	Female	23	95			
	Right	22	79	0.29	1	0.59
Symptoms	Left	17	79			
	Asymptomatic	20	126	11.8	1	0.0006
Visual acuity	Symptomatic	19	32			
	6/6 or better	19	84	1.9	1	0.38
Thickness of lesion	6/7.5 to 6/12	12	55			
	<1 mm	3	87	41.6	3	<0.0001
	≥1 to <2 mm	9	35			
	≥2 to <3 mm	11	23			
	≥3 mm	16	13			
	2.5±1.4	1.0±1.1	t=6.8			
Basal diameter of lesion	<3 mm	1	44	27.7	2	<0.0001
	≥3 to <5 mm	8	46			
	≥5 to <7 mm	7	37			
	≥7 mm	23	31			
		7.6±3.0	4.8±3.0			
Location of the lesion's anterior margin	Posterior to the equator	30	118	0.007	1	0.94
	Anterior to the equator	9	40			
Location of the lesion's posterior margin in relation to optic disc	Involving optic disc	11	10	17.8	2	0.0001
	Within 2 DD from optic disc	11	37			
	Over 2 DD from optic disc	17	111			
Location of the lesion's posterior margin in relation to foveola	Extending beneath foveola	3	16	4.7	2	0.0950
	Within 2 DD from foveola	14	31			
	Over 2 DD from foveola	22	112			
Retinal detachment	None	14	147	73.3	2	<0.0001
	Subretinal fluid ≤1 DD beyond lesion margin	17	9			
	Subretinal fluid >1 DD beyond lesion margin	8	1			
Orange pigment clumps on lesion‡	No	30	150	10.7	1	0.0011
	Yes	9	8			
Drusen on lesion‡	No	29	85	4.6	1	0.032
	Yes	10	73			
Black pigment clumps on lesion‡	No	33	139	0.088	1	0.77
	Yes	6	19			

*Mean values of variable are shown only for normally distributed variables recorded on a standard interval scale.

‡Variable assessed with reference to standard photograph.

DD=disc diameter, approximately 1.75 mm.

To simplify the presentation of our prognostic factor results we compiled a table (Table 3) showing the incidence of lesion enlargement through 2.5 and 5

years as a function of the presence or absence of the three parameters identified in our best Cox model (see preceding paragraph). This table is a con-

Table 2 Prognostic factor assessment by univariate Cox modelling

variable	beta coefficient	standard error of β	t	p
Retinal detachment	1.69	0.20	8.3	<0.0001
Thickness of lesion	0.64	0.10	6.7	<0.0001
Basal diameter of lesion	0.21	0.04	4.9	<0.0001
Location of lesion's posterior margin relative to optic disc	-0.74	0.19	3.8	0.0001
Symptoms	1.08	0.32	3.4	0.0007
Orange pigment clumps on lesion	1.23	0.38	3.2	0.0012
Drusen on lesion	-0.84	0.37	2.3	0.022
Age of patient	-0.02	0.01	1.9	0.052
Colour of lesion	-0.42	0.25	1.7	0.091
Visual acuity	-0.08	0.05	1.6	0.11
Location of lesion's posterior margin relative to foveola	-0.23	0.22	1.1	0.29
Black pigment clumps on lesion	0.30	0.44	0.67	0.51
Eye	-0.19	0.32	0.58	0.56
Sex	0.11	0.33	0.35	0.73
Location of lesion's anterior margin	-0.07	0.38	0.18	0.86

venient way of defining which melanocytic choroidal lesions are high risk for enlargement. From this table one can see that the five-year incidence of lesion enlargement for patients with none of these prognostic parameters was 5.8%, while that for patients with all three unfavourable parameters simultaneously was 90.6%.

Discussion

This study shows by survival analysis that the majority of melanocytic choroidal lesions classified as

naevi do not enlarge appreciably during five years of follow-up. In contrast, the majority of lesions classified clinically as melanomas do enlarge during a five year follow-up period. Neither of these findings is surprising.

Most of the results of our analysis by univariate prognostic factor agree with Gass's findings.⁸ Lesion thickness appeared to be a better indicator of growth potential than was lesion basal diameter in both Gass's series and in ours. Similarly, the presence of drusen appeared to be predictive of lesion dormancy in both series. Symptoms attributable to the lesion, prominent orange pigment clumps on the lesion's surface, and retinal detachment were also predictive of lesion enlargement in both series.

The predictive value of location of the lesion's posterior margin shown in this study was unexpected. The significance of location of the lesion's posterior margin in both univariate and multivariate models, however, suggests that this parameter may convey useful prognostic information about lesion enlargement. On the other hand this parameter may be significant only because it is more difficult for ophthalmologists to identify subtle enlargement of peripheral lesions than of posterior ones. Assessment of the prognostic value of this parameter in other data sets may clarify its true significance.

Although the best multivariate model for prediction of lesion enlargement in this group of patients was the three term regression presented in the 'Results' section, several other three-term regressions were of almost equivalent predictive value. It is certainly possible that an alternative model may prove to be a more appropriate and reliable regression for prediction of lesion enlargement in other studies of melanocytic choroidal lesions. The three parameters included in our model are not necessarily the most important ones in all patients with melano-

Table 3 Cumulative actuarial proportion of 197 melanocytic choroidal lesions which enlarged during follow-up as a function of the presence of identified prognostic factors

Prognostic Factors							
Symptoms	Thickness of lesion >1.5 mm	Retinal detachment	Number of prognostic factors present	2.5-year incidence of lesion enlargement (percentage)		5-year incidence of lesion enlargement (percentage)	
				rate	standard error	rate	standard error
Yes	Yes	Yes	0	4.1	2.3	5.8	2.8
			1	38.0	7.1	40.7	7.3
			1	35.8	6.5	54.1	7.7
Yes	Yes	Yes	1	66.1	8.5	81.0	7.4
			2	64.6	10.9	74.5	11.2
Yes	Yes	Yes	2	62.5	10.0	78.6	9.0
Yes	Yes	Yes	2	82.1	9.3	88.1	7.9
Yes	Yes	Yes	3	81.3	11.9	90.6	8.9

cytic choroidal lesions, nor are they necessarily the only important ones.

The findings of this study do not clarify the important question about whether mere recording of lesion enlargement is appropriate management of patients with suspected choroidal melanoma. The answer to this question will have to await the results of appropriately designed, comparative survival analyses of patients managed promptly after clinical diagnosis of choroidal melanoma versus those treated only after recording of lesion enlargement. Meanwhile our table showing the incidence of lesion enlargement as a function of the presence or absence of the three prognostic parameters identified by our best Cox model (Table 3) may prove useful to clinicians. Using this table a clinician can estimate the likelihood that a patient's melanocytic choroidal lesion will enlarge during up to five years of follow-up. If the estimated likelihood of lesion enlargement is high and the clinician elects to observe the patient rather than advise treatment, he will probably want to arrange for closely spaced follow-up evaluations. If, on the other hand, the likelihood of lesion enlargement appears to be low, the clinician may be more confident in arranging for longer intervals between follow-up examinations.

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Intraocular lens design and the inhibition of epithelium

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SUMMARY Of 1170 eyes implanted with posterior chamber lenses between 1981 and 1986 and having intact capsules at surgery, 1015 were examined two years after surgery, 741 were examined three years after surgery, and 308 were examined five years after surgery. At three years the capsulotomy rate for epithelium was 25% for 263 'lasergap' lenses, 2.4% for 296 convex posterior lenses, 8.2% for 73 planoposterior lenses with angulated loops. The highly significant difference for lasergap design, whether ridged, meniscus, or bossed, is of immediate interest to surgeons concerned with minimising the need for secondary capsulotomy. The two-year follow-up of soft hydrogel lenses suggested that these lenses also do not significantly retard the ingrowth of epithelium.

There are two main mechanisms whereby the posterior lens capsule may become opacified after extracapsular cataract surgery.¹⁻⁴ One is the migration of epithelial cells on to the capsule, with proliferation into Elschnig's pearls (epithelium). The other involves lens epithelial metaplasia into myofibroblasts that induce fibrosis and contracture of the capsule (fibrosis).

Epithelium once within the visual axis will reduce visual acuity to less than 6/36 within six months. Without a lens implant about 45% of patients require secondary capsulotomy within three years of surgery.⁴⁻⁷ The incidence is reduced by the implantation of an intraocular lens, but by different degrees according to design.

Fibrosis reduces vision very slowly,³ being a smooth less opaque proliferation which may be enhanced by convex posterior lenses of polymethyl methacrylate.^{1,12} Fibrosis also occurs more rapidly in association with inflammatory syndromes.⁸ Without lens implantation its incidence as a cause of secondary capsulotomy is approximately 2%.

This paper considers solely epithelium, and the influence of implant design on the need for secondary capsulotomy.

Materials and methods

All patients who had undergone extracapsular cataract extraction with an *intact capsule* at surgery and insertion of a posterior chamber implant between 1981 and 1986 were called for examination two, three, and five years after surgery. Perforating injuries and secondary implantations were excluded. The age range at surgery was 29 to 94 (mean 74) years. Of the 958 patients (1170 eyes) called for review two years after surgery, 18 had moved from the district, 122 had died, and 818 were examined. Of these 197 had undergone bilateral surgery, making the total number of eyes examined 1015. By three years the death toll had risen to 17%, 17 patients (19 eyes) were untraceable, and 619 patients (741 eyes) were examined. Four hundred and fifty-eight operations were eligible for five-year follow-up, having been performed prior to 1984. Of these, 128 were lost because the patient had died (28%), 22 eyes (21 patients) were untraceable, and 308 eyes were examined.

The lenses examined at two years were grouped (a) as 182 planoposterior convex anterior (CA) lenses; (b) as 431 reversed optic or convex posterior (CP) lenses; (c) as 320 lasergap lenses; and (d) as 82 biconvex hydrogel lenses made of polyhydroxyethyl methacrylate (38% water), the design of which has

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Table 1 *Styles of lenses analysed: (a) convex anterior (CA), (b) convex posterior (CP), (c) laser gap, (d) biconvex hydrogel*

Manufacturer	Code and style	Placement	Haptics	Number examined		
				2 yr	3 yr	5 yr
(a) Rayner	487 Boberg-Ans	Iridocapsular	Solid PMMA	99	96	79
Iolab	103Q Sinskey	Ciliary Sulcus	Polyprop. loops	83	73	68
(b) Rayner	850 Pearce	Sulcus 1981-3	Polyprop. loops	431	296	161
		Capsule 1984-6				
(c) Cilco	JFILRU Jaffe	Capsule	PMMA loops	156	115	0
Prec. Cosmet	8661 Kratz	Capsule	PMMA loops	44	43	0
Prec. Cosmet	9310	Capsule	PMMA loops	56	42	0
Rayner	860	Capsule	Polyprop. loops	35	34	0
Iolab	707G	Capsule	Polyprop. loops	21	21	0
Pharmacia	Laser spacer	Capsule	Polyprop. loops	8	8	0
(d) Alcon	PC12 Barrett	Capsule	Solid hydrogel	82	13	0

PMMA = polymethyl methacrylate.

Table 2 *Incidence of capsulotomy for epithelium among laser gap lenses at three years' follow-up*

Manufacturer	Laser space design		Number of eyes	Number of capsulotomies	(%)
Cilco	JF1	Circumferential ridge	115	36	31
Prec. Cosmet	8661	Four bosses	43	9	21
Prec. Cosmet	9310	Circumferential ridge	42	13	31
Rayner	860	Meniscus	34	5	15
Iolab	707G	Circumferential ridge	21	3	14
Pharmacia		Circumferential ridge	8	0	0

Table 3 *Comparative need for capsulotomy for epithelium among eyes examined*

	Examination								
	At 2 years			At 3 years			At 5 years		
	Eyes	Caps.	%	Eyes	Caps.	%	Eyes	Caps.	%
Boberg Ans CA	99	2	2.0	96	4	4.2	79	8	10.1
Sinskey CA	83	4	4.8	73	6	8.2	68	9	13.2
Pearce CP	431	4	0.9	296	7	2.4	161	9	5.6
Laser gap	320	52	16.2	263	66	25.0	0		
Hydrogel CP	82	14	17.1	13	4	30.8	0		
No implant	88	20	22.7	80	34	42.5	67	31	46.2

been well documented elsewhere." Details of the styles, placements, and follow-up are shown in Table 1. All flexible loops were angulated forwards. The solid hydrogel haptics were also angulated forwards.

The criteria for a need for capsulotomy were significant capsular opacification reducing the visual acuity to less than 6/12 or a visual acuity of 6/9 or 6/12 but associated with symptoms from mild opacification. Whenever a capsulotomy had been performed, a note had been recorded specifically on whether the reason for capsulotomy was ingrowth of epithelium or fibrosis of the lens capsule. All eyes were examined as to whether visual loss was occurring due to capsular opacification or whether secondary capsul-

otomy had been performed in the past. In this study only the findings of those eyes requiring or having required capsulotomy for epithelium were recorded.

Results

The need for capsulotomy before three years had passed among laser gap lenses is shown in Table 2. These were lenses designed to provide a space behind the lens optic for later YAG laser treatment, and the laser space design is also indicated in the table. Although variation occurred among different styles, the numbers were too few to be significant, and for further comparison these eyes were grouped together as 'lasergap' lenses.

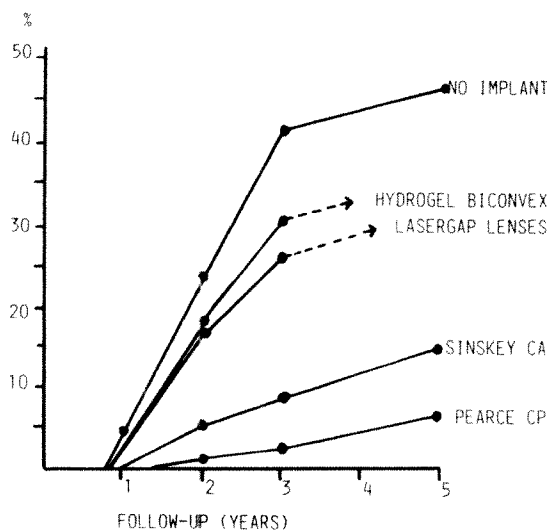


Fig. 1 Incidence of capsulotomy for epithelium

The comparative incidence of capsulotomy for epithelium among eyes that had intact capsules at surgery when examined two, three, and five years later is shown in Table 3. Eighty-eight eyes from an earlier period⁷ operated on without lens implantation and examined similarly have been included for comparison. Fig. 1 compares the incidences in graphic form.

Age was not found to be a factor in determining the incidence of capsulotomy (the mean age was 73 years), and there were no other clinical factors relevant to ingrowth of epithelium apart from implant style, which was highly significant. Just two years after surgery 16% of the 320 lasergap lenses were associated with capsulotomy compared with 1.6% of the other 613 polymethyl methacrylate lenses. Convex posterior lenses had the smallest incidence of capsulotomy of 1% at two years, rising to 5.6% at five years. The hydrogel lenses although biconvex, had an incidence of capsulotomy of 17% two years after surgery.

Discussion

The capsulotomy rate for about three years of follow-up has been reported as 5%,¹⁰ 8%,¹¹ 9%,^{2,12} 15%,^{11,13} 18%,^{2,14} 24%,⁵ and 29%.² The discrepancies may be related to any of a number of factors:

(1) *Age of the population sampled.* It has been suggested that a disproportionate number of younger adults will increase the mean incidence of epithelialisation.¹² However, in the present study at three years, although 22% of eyes requiring capsulotomy for epithelium were in patients under the age of 65, it

was also found that 26% of eyes were in patients over the age of 80 at the time of extracapsular cataract extraction.

(2) *Structure of the study.* An incidence prepared for a mean follow-up period will be skewed downwards by inclusion of numbers with insufficient follow-up, since epithelialisation of the lens capsule is rare before 15 months. We attach great importance in reporting only on patients who have passed the two, three, and five year stage after surgery.

(3) *Accounting for all patients undergoing surgery.* Many authors report the number of eyes showing opacification per eyes operated on without specifying the number unavailable because of death of being too infirm to attend or possible removal to a different district for capsulotomy. This method may indicate the likelihood of a patient's requiring a second operation in a particular surgeon's practice, but it does not reflect the true incidence to be expected for a given implant.

(4) *Style of lens.* CP lenses^{2,14,15} and angulated haptics¹¹ are associated with less opacification than those which are planoposterior or uniplanar. Our results support this finding, with an incidence of epithelium at three years of only 2.4% for CP lenses compared with 8.2% for the Sinskey CA lenses. Our results do not support the suggestion first by Hoffer¹⁶ and later by Jaffe¹⁷ that a circumferential ridge on the posterior aspect of the lens will significantly retard the ingrowth of epithelium.

It should be remembered, however, that tight contact of the posterior capsule against CP lenses may favour the development of fibrosis,^{1,18} especially in the presence of inflammatory syndromes which may result from sulcus placement or association with glaucoma surgery.² In a separate study we found that 49 of the eyes examined at three years had been associated with the glaucoma triple procedure or past glaucoma surgery. Ten of these had required capsulotomy for fibrosis (eight out of 28 CP lenses). With these 49 glaucomatous eyes excluded the incidence of capsulotomy for fibrosis at three years was found to be 10 of 268 CP lenses, two of 160 CA lenses, and four of 251 lasergap lenses. After exclusion of the Boberg Ans lenses, which are now obsolete, and the glaucomatous eyes, this gave a combined incidence for capsulotomy at three years of 6.3% (17 out of 268) for CP lenses, 8.7% (six out of 69) for Sinskey CA lenses, and 26.7% (67 out of 251) for laser gap lenses.

(5) *Lens position.* Capsule fixation may have a lower incidence of opacification than sulcus fixation,¹⁰ but we do not consider epithelium to be seriously influenced by position. We believe that the optic design is more relevant.

The conclusions to be drawn from this study are, first, that surgeons who continue with laser gap

lenses, even if capsule fixated, subject themselves to an unnecessary work load in caring for capsular opacification. Secondly, CP lenses markedly inhibit epithelial ingrowth, so that biconvex or planoconvex designs should be encouraged. Thirdly, hydrogel lenses behave differently. Although these soft implants may have theoretical advantages over hard lenses in more closely mimicking the properties of living tissue and being hydrophylic, they do not significantly retard the ingrowth of epithelium even when initially positioned with a tight contact against the posterior lens capsule.

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Medical and surgical management of spontaneous hyphaema secondary to immune thrombocytopenia

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SUMMARY The medical and surgical management of an unusual case of spontaneous 'black ball' hyphaema complicated by secondary haemorrhage, raised intraocular pressure and corneal blood staining, and secondary to immune thrombocytopenia is presented. The literature is reviewed with particular reference to the aetiology and treatment of spontaneous hyphaema and the role of intravenous immunoglobulins in the preoperative management of patients with thrombocytopenia who present for routine or emergency ocular surgery.

Spontaneous hyphaema is relatively uncommon. Only three cases have been reported of its association with thrombocytopenia by Graves in 1837,¹ by Werner and Adlerkreutz in 1931,² and recently by Ackerman *et al*, who reported a case of spontaneous vitreous haemorrhage associated with thrombocytopenia in which a secondary hyphaema developed.³

Case report

The patient, a 59-year-old Caucasian woman, presented with a three-day history of a red, uncomfortable left eye and diminished left visual acuity. There was no history of trauma. Her visual acuity before onset of symptoms was 6/6 right and 6/9 left. The patient had been referred to the haematology clinic in 1984 with thrombocytopenia. Investigations revealed a leucocyte count $7.1 \times 10^9/l$ and a platelet count $85 \times 10^9/l$. The white cell differential count was normal. Her antinuclear factor was positive and the DNA binding 35 units/ml (normal = 1-25). A bone marrow aspirate was of normal cellularity with an increased number of megakaryocytes, consistent with peripheral destruction or sequestration of platelets. Blood coagulation tests gave normal results and there was no splenomegaly. Although indirect immunofluorescence tests were negative for platelet antibodies, these findings were compatible with a

diagnosis of chronic immune thrombocytopenia (ITP), possibly associated with systemic lupus erythematosus, despite the absence of supporting clinical features.

On admission to hospital her visual acuity was 6/9 in the right eye and perception of light in the left eye. There was a subtotal left hyphaema of approximately 80%. The corneal epithelium was oedematous and the intraocular pressure raised (75 mm Hg). The platelet count was $49 \times 10^9/l$.

The patient was advised bed rest and received topical timolol drops and intravenous acetazolamide. Acetazolamide was continued orally. During the first 24 hours there was a modest fall in the intraocular pressure followed the next day by further bleeding into the anterior chamber. The patient developed a total or 'blackball' hyphaema (Fig. 1), with a further increase of the intraocular pressure (70 mm Hg). Six units of platelets were transfused over each of the first three days. On the third day, in an attempt to secure haemostasis and with evidence of further anterior chamber haemorrhage, oral prednisolone (40 mg daily) was begun, together with an intravenous infusion of immunoglobulins over three days (Sandoglobulin 400 mg/kg body weight). Daily platelet counts were obtained, and their changes in relation to treatment are shown in Fig. 2. There was no reduction in the size of the hyphaema and the intraocular pressure remained raised (50 mm Hg). Surgical intervention was indicated with the develop-

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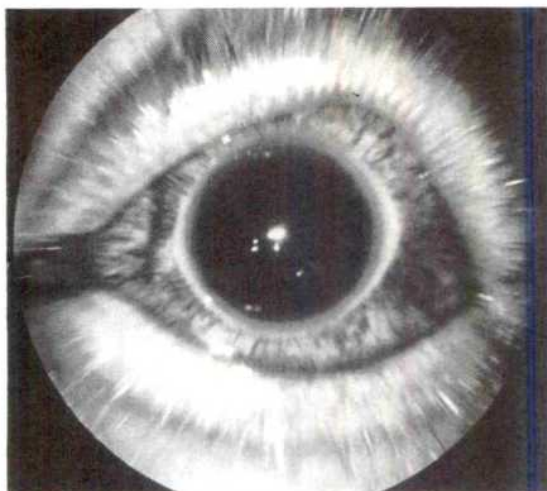


Fig. 1 Total hyphaema shortly after admission.

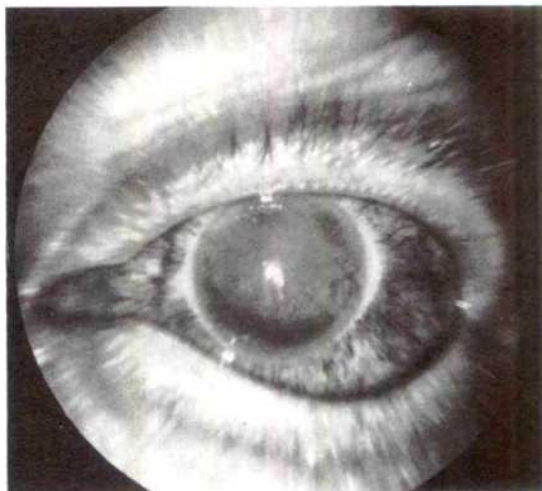


Fig. 3 Second postoperative day. Small residual blood clots can be seen adherent to the corneal endothelium.

ment of corneal blood staining and evidence of early organisation of the clot.

Prior to surgical evacuation the patient received the antifibrinolytic agent tranexemic acid, 1 g three times a day. A Simcoe irrigation/aspiration cannula was introduced through a 3 mm limbal corneal incision, and approximately 90% of the hyphaema was aspirated. A small peripheral iridectomy was made at the 3 o'clock position directly below the corneal incision. In the initial postoperative period there were several small residual blood clots adherent

to the endothelium, and the cornea was partially decompensated with corneal epithelial oedema (Fig. 3). The intraocular pressure, however, remained normal, and there was no further anterior chamber haemorrhage. The several small residual blood clots adherent to the endothelium were reabsorbed over the ensuing weeks, and at a subsequent review five months later her corrected visual acuity was 6/12. The corneal epithelial oedema had resolved and the intraocular pressure was normal.

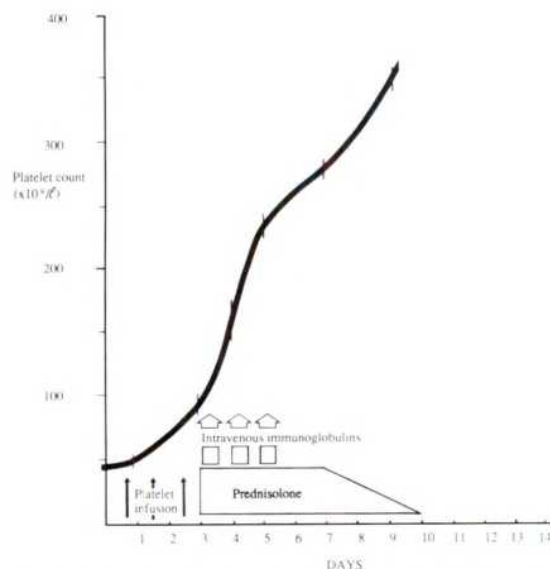


Fig. 2 Changes in platelet count in response to treatment.

Discussion

Anterior chamber haemorrhage is usually associated with ocular trauma. Spontaneous hyphaema is relatively uncommon, being noted mainly in younger patients. Spontaneous haemorrhage may occur from abnormal anterior chamber vessels associated with iris melanoma, retinoblastoma, juvenile xanthogranuloma, or rubeosis secondary to diabetes mellitus or Fuchs's uveitis syndrome.⁴⁻⁶ Fibrovascular membranes of retrolental fibroplasia, retinoschisis, and persistent primary vitreous may also bleed into the anterior chamber.⁷ Haemorrhage from iris neovascular tufts near the pupillary frill was first reported in 1973.⁷ Haemorrhage has also been noted in cases of anterior uveitis associated with herpes zoster, diabetes mellitus, and Beçet's syndrome.⁸ Ormerod and Egan in 1987 reported 16 cases of spontaneous hyphaema and corneal haemorrhage as a complication of microbial keratitis.⁹ Spontaneous hyphaema has also been noted in conjunction with blood dyscrasias, notably leukaemia, haemophilia, sickle cell anomalies, and

malignant lymphoma.¹⁰ Kzgeler *et al* reported a case of spontaneous hyphaema secondary to ingestion of aspirin and alcohol,¹¹ related presumably to a reduction in platelet function.

Immune thrombocytopenia (ITP) is a heterogeneous syndrome of unknown aetiology characterised by a reduction in the platelet count, normal or increased number of bone marrow megakaryocytes, and a shortened platelet life span. In a variable proportion of patients (3-16%) it may be an early manifestation of systemic lupus erythematosus (SLE).¹² An increased frequency of HLA DRW2 and a high female predominance also link the two diseases.¹³ There is evidence that peripheral destruction of platelets is responsible for the thrombocytopenia in SLE.¹⁴ The mechanism may involve either antiplatelet antibodies or immune-complex mediated destruction by reticuloendothelial cells.

Conventionally the primary treatment of ITP has been systemic corticosteroids giving a remission rate of up to 80%. There is a high relapse rate, and in these patients together with those refractory to steroids splenectomy is sometimes indicated. More recently commercial preparations of intravenous immunoglobulins have been introduced as a novel treatment of patients with ITP. Preliminary studies by Imbach *et al*¹⁵ showed that some children with ITP respond to large doses of immunoglobulins, and this was confirmed by Bussel *et al*.¹⁶ High doses of intravenous immunoglobulins have also been shown to produce a rapid and predictable rise in the platelet count of adults with acute or chronic immune thrombocytopenia.¹⁷⁻¹⁸ The exact therapeutic mechanism remains uncertain, though a number of interesting theories have been proposed, of which the most popular is the blockade, by immunoglobulins, of the macrophage Fc receptors.¹⁸⁻²⁰

The medical management of uncomplicated hyphaema has been a subject of a number of studies. Edwards and Layden in 1973 reported no difference between monocular and binocular patching.²¹ Bed rest and sedation confers no statistically significant benefits on reabsorption of hyphaema or secondary bleeding rates.²²⁻²³ The reported incidence of the secondary bleeding rate varies widely (6-38%), with an overall approximate rate of 25%.²² The incidence is directly related to size of hyphaema, indirectly related to the patient's age, and is associated with concurrent aspirin ingestion.²⁴ The antifibrinolytic drugs aminocaproic acid and tranexamic acid have been recently advocated to reduce the incidence of secondary haemorrhage.²⁵⁻²⁶ They act principally through competitive inhibition of plasminogen activator, preventing conversion of plasminogen to plasmin, maintaining the integrity of the fibrin clot, and reducing the opportunity of the damaged vessels

to bleed again. Systemic steroids²⁷ and oestrogens²⁸ have been largely discarded in the routine management of hyphaema.

There was a modest transient rise in the platelet count in response to the initial platelet transfusions. However, with the continued anterior chamber haemorrhage and the prospect of surgery it became apparent that intravenous immunoglobulins were indicated to secure and maintain adequate haemostasis. The sustained rise in platelet count was almost certainly directly attributable to the intravenous immunoglobulins. Transfused platelets in the setting of immune thrombocytopenia have a very short lifespan,²⁹ and steroids often take up to two weeks to induce a rise in platelet count.³⁰ There is also evidence of a cumulative effect of combining steroids and immunoglobulins in producing a higher and more sustained rise in the platelet count.³¹ The ability of commercial high-dose preparations of immunoglobulins to produce a dramatic correction of thrombocytopenia enables otherwise hazardous emergency surgical procedures to be carried out safely.^{17,32-33}

For small hyphaemas conservative medical management provides the best overall results, but for larger hyphaemas the indications for surgical intervention are: (1) sustained elevation of the intraocular pressure unresponsive to treatment; (2) microscopic corneal blood staining; and (3) evidence of organisation of the clot, with the potential for the formation of peripheral anterior synechiae.³⁴⁻³⁵

Surgical evacuation of hyphaema may present difficulties. It has been suggested that the optimum time for evacuation is four days, which allows for optimal clot retraction while avoiding the problems of clot organisation and integration with adjacent structures.³⁶ Many different surgical procedures with varying degrees of success have been described, including, irrigation with fibrinolytic agents, cryo-extraction, viscoelastic extrusion, ultrasonic emulsification, and the use of vitrectomy instrumentation.³⁶⁻⁴¹ The use of the Simcoe irrigation-aspiration cannula introduced through a small corneal incision proved to be very satisfactory. The risk of prolapse of intraocular contents was reduced by the small incision. The variable infusion pressure ensured the maintenance of the anterior chamber depth to protect the corneal endothelium. In addition there was the opportunity to tamponade any subsequent haemorrhage by alteration of the infusion flow rate.

CONCLUSIONS

A haemorrhagic diathesis should be considered in all cases of atypical spontaneous hyphaemas. If a surgical procedure is indicated, in the presence of immune thrombocytopenia, intravenous immunoglobulins may have a useful role in the management.

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Spontaneous recovery of vision following an orbital haemorrhage

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SUMMARY A 73-year-old man presented to casualty with a penetrating orbital injury and total loss of vision in the affected eye. He subsequently spontaneously recovered full vision. We stress the need for frequent assessment of vision before considering potentially hazardous surgical intervention.

Blindness has been reported following penetrating and blunt orbital trauma,¹⁻⁴ but to our knowledge spontaneous and complete recovery of vision has never been reported.

Case report

A 73-year-old man presented to an eye casualty department 45 minutes after having been stabbed in the supratrochlear region of his right orbit with a screwdriver. The visual acuity was, on the right, no perception of light, and on the left 6/12. On examination there was 5 mm of proptosis and a complete ptosis on the right side. Movements of the right eye were generally restricted. There was an absolute right afferent pupillary defect, with a normal consensual response. Both fundi were normal.

One hour after injury the patient's right visual acuity was counting fingers in the temporal periphery. One hour 10 minutes after the injury the right visual acuity was 3/24, and one hour 55 minutes after it the acuity was 6/12, with a pinhole 6/9. Twenty-four hours after the injury the findings on the right were: V A 6/9, 2 mm of proptosis, normal pupil, extraocular movements full, no ptosis, fundus normal.

Six months later his best corrected visual acuity on the right was 6/9 -3, with no abnormalities detected on that side.

Discussion

A 73-year-old man presented to the casualty department with penetrating orbital trauma and total loss of vision in the affected eye. He subsequently spontaneously recovered full vision.

The cause of visual loss may have been due to compromise of the retinal, choroidal, or optic nerve circulation. We consider that this case represents an episode of optic nerve malfunction. Lederman² reported loss of vision following surgical treatment of a zygomatic-orbital floor fracture. His case had a normal electroretinogram and an abnormal visual evoked response in the affected eye, implying a compromised optic nerve.

Optic nerve malfunction may be due to compression of the pial plexus of vessels or direct compression of the axons. Feist *et al*⁴ reported a case of presumed direct optic nerve injury with spontaneous but incomplete recovery.

Central retinal artery occlusion has been reported following both blunt and penetrating trauma.^{5,6} Kroll's experimental work⁷ on monkey retinas has shown that ophthalmoscopically visible fundal changes occur 15 minutes after central retinal artery occlusion. In our case, even though total blindness was recorded for only 15 minutes the blindness probably persisted for longer. Thus it seems unlikely that arterial occlusion was a cause of the visual loss.

The ptosis could have been caused by a third nerve palsy involving the superior branch of the nerve. This

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would be consistent with the preservation of the consensual pupillary response, since the pupillary fibres are carried in the inferior branch.¹⁰

Blindness following orbital trauma has been treated in a number of ways. A lateral canthotomy was performed to immediate and good effect by Katz *et al* in two cases of visual loss following orbital haemorrhage, when vision improved after three and a half and four and a half hours of total blindness.¹ In a case of orbital haemorrhage and visual loss Brooks and Finkelstein proceeded to a superolateral orbitotomy after computerised tomography had revealed an intraorbital haematoma.⁵

A lateral canthotomy should be immediately undertaken in a patient with a normal fundus and visual loss due to an orbital haemorrhage. If this does not produce significant sustained visual recovery, urgent computerised tomography is indicated in order to decide on the appropriate surgical approach. There is time to organise these investigations, for Katz *et al* have shown that the optic nerve can withstand prolonged ischaemia.¹

The present case shows that visual loss following orbital haemorrhage may end in spontaneous recovery. We stress the need for frequent assessment of vision before considering potentially hazardous surgical intervention.

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Heterotopic brain tissue in the orbit: case report

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SUMMARY A case of heterotopic brain tissue within the orbit is reported. Previously reported cases of this condition are reviewed, with particular reference to the pathogenesis and visual outcome.

The findings of heterotopic brain tissue within the orbit is extremely rare. A report of such a case follows.

Case report

A 2-year-old girl presented with a history of a slowly expanding mass in the region of the right medial canthus. The patient was born by a normal vaginal delivery after an uncomplicated pregnancy. Her parents noticed a small swelling in this region at birth. She has been otherwise well and has four normal older siblings.

Examination revealed a palpable swelling at the right medial canthus with shortening of the right palpebral aperture (right 20 mm and left 23 mm). The right medial canthus was displaced laterally and inferiorly (Fig. 1). There was no proptosis. Fixation was central and steady with each eye, and the eyes were orthotropic to cover testing. Eye movements

were full. She was emmetropic in both eyes and both fundi were normal.

CT scan showed a plaque-like mass involving the anteromedial portion of the right orbit (Fig. 2), displacing the medial wall towards the midline. No communication with the brain or cranial cavity was demonstrated. The clinical diagnosis at this stage was of an orbital dermoid.

At 2½ years of age the patient underwent a right orbitotomy via a craniofacial approach (coronal incision from right to left preauricular regions with mobilisation the anterior flap so as to expose the orbits from above). The periorbital were slightly thickened but stripped easily from the roof and medial wall of the orbit. The mass was entirely located within the periorbital. No bony defects were found in the roof or medial wall of the orbit. On opening the periorbital a reddish, friable, poorly encapsulated mass was found. It extended round both the superior oblique and the medial rectus and posteriorly beyond the equator of the globe. A macroscopically complete excision of the tumour mass was undertaken.

Histological examination showed masses of mature neuroglia with moderate numbers of normal looking neurons (Fig. 3). Extensive spotty calcification was seen, often round blood vessels. There was no surface differentiation to ependyma or choroid plexus, and non-neural elements were not found.

Postoperatively there was considerable periorbital oedema, which settled over one week. Visual function and ocular motility were both normal. Three months postoperatively the patient remained well and there was no evidence of recurrence of the mass.



Fig. 1 Preoperative appearance showing swelling displacing medial canthus laterally and inferiorly.

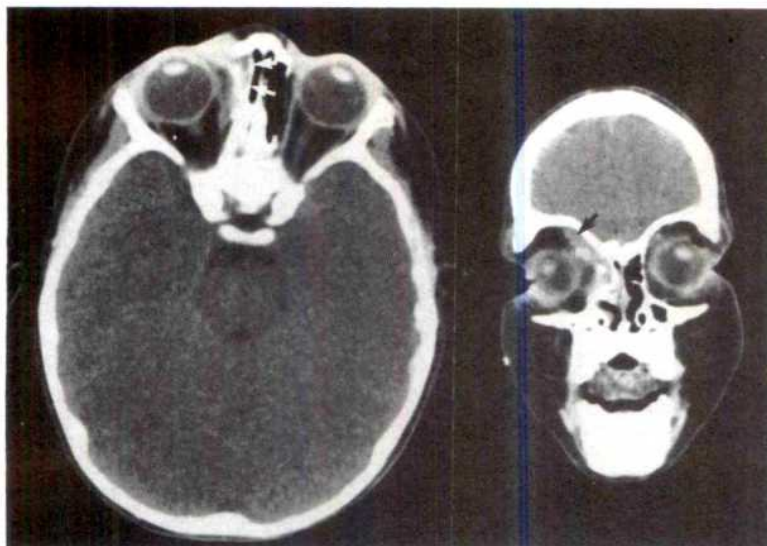


Fig. 2 Left: Horizontal CT scan demonstrating soft tissue mass in anteriomedial aspect of right orbit. Medial wall of orbit is displaced towards the midline but is intact (arrows). Right: Coronal CT scan showing mass (arrow) in the superomedial orbit with intact orbital roof and medial wall.

Discussion

Heterotopic brain in the orbit is very rare. Only four definite¹⁻⁴ and two possible cases^{5,6} have been reported. (Two cases of limbal dermoids containing heterotopic brain have also been described.^{7,8}) Encephaloceles and meningoencephaloceles with a demonstrable connection with the brain or meninges

are more commonly recognised within the orbit.⁹

Extracranial heterotopic brain tissue has been described in a number of other sites in the head and neck, most commonly in the nasal region. These are generally known as nasal gliomas, and over 100 cases have been reported.¹⁰ Less frequently reported sites are naso- and oropharynx,¹⁰⁻¹⁵ palate,¹⁶ tongue,¹⁷ scalp,^{18,19} and neck.²⁰

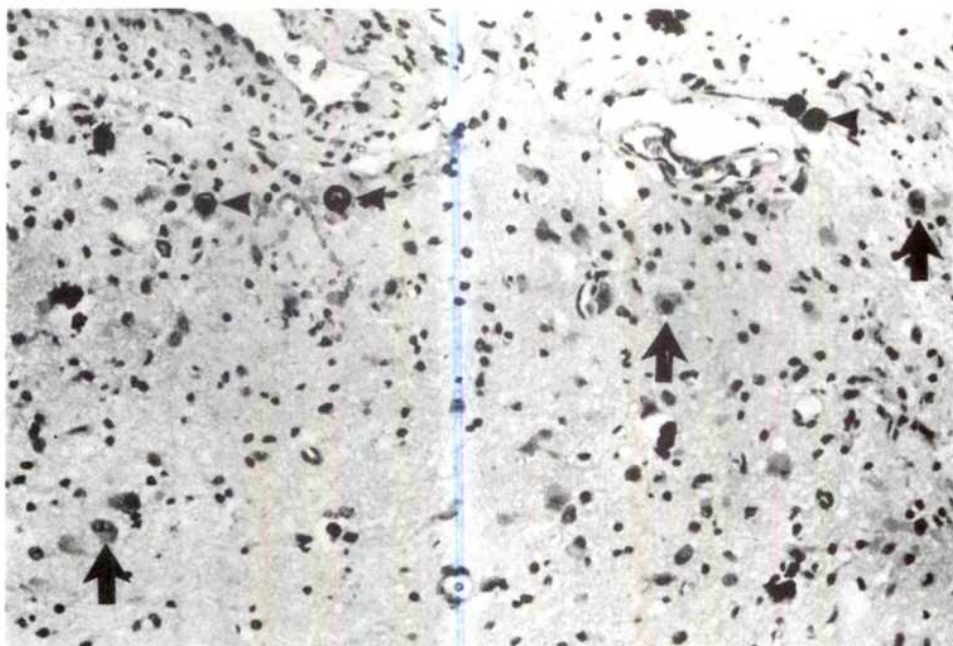


Fig. 3 Mature neuroglia with neurons (arrows) and focal calcification (arrowheads). (H and E, $\times 200$).

Table 1 Review of reported cases with visual outcome.

No	Author	Year	Orbital lesion	Vision
1	Acers ¹	1965	Encephalocele	Not recorded
2	Rodrigues and Shannon ²	1977	Meningo-encephalocele	'Normal'
3	Vaquero <i>et al.</i> ¹	1980	Intraorbital and intracranial glial hamartoma	6/60, optic atrophy
4	Call and Baylis ²	1980	Cerebellar heterotopia	'Decreased' afferent pupil defect
5	Newman <i>et al.</i> ³	1986	Heterotopic brain	1/60, dense amblyopia
6	Wilkins <i>et al.</i> ⁴	1987	Heterotopic brain	Not recorded
7	Elder <i>et al.</i>	1988	Heterotopic brain	Normal fixation pattern

The genesis of heterotopic brain is not clear, and a number of theories have been suggested. These include (1) herniation of the intracranial contents through a skull defect which subsequently closes, leaving no direct connection between the heterotopic focus and the brain; (2) early separation of neuroectodermal rests; (3) teratomatous malformation with proliferation of a single cell line; (4) true astrocytomas; and (5) migration of glial cells along the olfactory nerves during embryogenesis.^{3,9,10,21} Only the first theory is widely accepted.

In this case there was no evidence of a bony defect nor of any connection with the cranial cavity. In four of the previously reported cases^{1,3,4,6} a bony defect was found, though intact dura mater separated the heterotopic brain from the cranial contents. In the fifth case² the mass was in the posterolateral orbit adjacent to the superior orbital fissure, and post-operatively there was fluid leakage thought to be cerebrospinal fluid. It is not clear whether this leakage was due to the surgery or represented a pre-existing connection with the subarachnoid space. The report of the remaining case⁵ describes radiological evidence of adjacent bony erosion but does not provide any operative findings on the integrity of the orbital walls.

Histological examination in this case showed mature glia and neurons, with extensive calcification, which was probably secondary and is common in malformations.

In a previous case report³ striated cells were intermixed with glial tissue. This has been interpreted as local invasiveness. However, striated cells have been found in heterotopic brain in sites remote from normal muscle and in glial cell cultures.²²

These lesions are slow growing and have not shown malignant features.^{3,9} Further growth after incomplete resection has been described in two

cases.^{3,4} In both of these cases the recurrent was in part cystic, and repeated operations have been required to remove the tumour mass. Histological examination after subsequent operations revealed tissue identical to original specimens. As yet there has been no sign of recurrence of the mass in our patient, though the follow-up is only three months.

The visual outcome in these cases has been variable (Table 1). In one case visual loss was presumably due to strabismic amblyopia³ and in another possibly due to optic atrophy.¹ In our case the patient is too young for reliable estimation of visual acuity, though her visual development appears to be normal.

Given the potential for visual loss and the tendency of the tumour to recur after attempted resection, frequent ophthalmological review and early surgical intervention in the case of recurrence are recommended.

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Correspondence

Fundus changes in mesangiocapillary glomerulonephritis

SIR, I read the article by Josephine Duvall-Young, Mary MacDonald, and Nicol McKechnie on the fundus changes in (type II) mesangiocapillary glomerulonephritis.¹ They suggest from the title of the article and also in their discussion, that they have a clinicopathological correlation between the appearance of drusen in the eye and changes in Bruch's membrane and the choriocapillaris with ultrastructural similarities to the electron dense deposit seen in type II diseased glomeruli. On reading the article I was surprised to see that the histopathology was carried out on an eye which had had a central vein occlusion followed by a rubeotic glaucoma and then further by a bullous exudative retinal detachment. Clinically the other eye, which was not examined histopathologically, had drusen.

The article states that it has demonstrated involvement of the choriocapillaris and Bruch's membrane and is showing a clinical correlation with drusen-like spots in the fundus. This is definitely not the case. The drusen-like spots were in the left eye and they did histopathology in the right eye. The right eye had a central vein occlusion which had gone on to a rubeotic glaucoma and then further on to a bullous exudative retinal detachment. It could be that the fibrinoid-like material which they found in Bruch's membrane and the involvement they demonstrated in the choriocapillaris are a feature more of someone who has had a central vein occlusion, rubeotic glaucoma, and a subsequent exudative retinal detachment rather than a specific histopathological feature of type II glomerulonephritis. A study of a similarly affected eye in a patient without this specific renal condition will have to be undertaken as a control before such a conclusion is valid.

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Reference

- 1 Duvall-Young J, MacDonald M, McKechnie N. Fundus changes in (type II) mesangiocapillary glomerulonephritis simulating drusen: a histopathological report. *Br J Ophthalmol* 1989; 73: 297-303.

SIR, The study of the eye of the patient with mesangiocapillary glomerulonephritis which was recently published showed deposits in the choriocapillaries and Bruch's membrane which was very dense on electromicroscopy. The deposit was very extensive and quite unlike any other which has been previously described in those areas. Clinically the other eye showed drusen-like deposits and our conclusion was that the finding in the enucleated eye correlated with the clinical finding in the fellow eye. Mr

Beaumont's suggestion that the study of the eyes of patients with vein occlusion and rubeotic glaucoma would have been valuable is valid. However, in our experience of examining large numbers of enucleated eyes at least one third of which would have had such conditions, we have never seen these deposits. The conclusion then would be either that the deposits are specific for MCGN (type II) or that this is an uncommon and possibly unique form of deposit in rubeotic glaucoma. We favour the first conclusion for two reasons. The first reason is described in the paper and is that the deposit is very like the deposit in the electromicroscopy of the kidney. The second reason is that following the published investigations we have studied a group of MCGN patients by clinical methods and have found a previously undiscovered deposit at the level of Bruch's membrane. These findings have been recently accepted for publication by your journal.

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Day case cataract surgery

SIR, We read with interest the article on day case cataract surgery by Watts and Pearce,¹ as we indeed support the concept of day stay surgery. However, we feel that some of the statements in this report deserve examination.

Firstly, we would like to endorse the statement that selection of patients is critical when considering this type of surgery. However, there is mention neither of the criteria for patient selection nor the status of the doctor asking the relevant questions. Far greater detail should have been provided on the degree of systems impairment in the 16 ill patients who were subject to this approach. Any significant degree of hypertension or diabetes, for instance, requires preoperative assessment and intraoperative management.

The statements regarding 'our techniques for anaesthesia' which 'obviate the need of an anaesthetist' suggest a purely local anaesthetic technique. We thought this approach disappeared a generation ago. A dose of temazepam 10 mg orally would have minimal beneficial effect for the patient, as this drug is not known for its antianxiety or amnesic properties. The presence of an anaesthetist means that low doses of an appropriate sedative/tranquilliser may be given, even to the elderly, to allow for a relaxed, calm state in which the patient is less likely to move, especially during the peribulbar injection of local anaesthetic. Furthermore, operative 'monitoring' should be considered. The surgeons were delivering a drug (oxygen) - without any monitoring - even to patients with emphysema. Appropriate monitoring with a pulse oximeter sets a baseline for cardiorespiratory performance and detects any untoward change, which can then be managed immediately by a practitioner qualified to do so. An electrocardiograph will detect any vagal effects resulting from the local anaesthetic injection and ocular or intraocular manipulation. Continuous non-invasive blood pressure readings are mandatory, especially when the patient's blood pressure is excessively high, as this may produce untoward systemic effects, and may even be a factor predisposing to expulsive choroidal haemorrhage.

There is no detail on 'patient satisfaction': did 33 of 40 patients actually refuse day case surgery for their second eye? Also the 5% incidence of posterior capsular rupture seems excessively high – could this be attributed to the technique? Finally, what would the surgeons have done in the recognition and management of any possible anaphylactic drug reaction?

We noted that the one patient who refused day only surgery was then offered only a general anaesthetic. We would argue for the presence of an anaesthetist at all cataract surgery, the use of appropriate low dose intravenous sedatives/hypnotics where indicated, and full monitoring techniques, which enable the selection criteria to widen to include almost every cataract patient. This assisted local anaesthetic (ALA) technique has been used successfully in our hands for many years now with minimal complications and great patient comfort.¹

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- 1 Watts MJ, Pearce JL. Day case cataract surgery. *Br J Ophthalmol* 1988; **72**: 897–9.
- 2 Francis IC, Schumacher RS, Haylen MJ. Assisted local anaesthesia for cataract surgery (ALACS). *Aust NZ J Ophthalmol* 1987; **15**: 185–91.

SIR, We are grateful to Haylen, Schumacher, and Francis for their comments on our paper on day case cataract surgery and interested to hear of their different anaesthetic technique for day case patients.

We are certainly aware of the use of 'assisted local anaesthetic (ALA)' techniques, in which an anaesthetist gives intravenous sedatives and hypnotics in conjunction with local anaesthesia, and indeed use it regularly on patients staying overnight in hospital. However, for patients undergoing day case surgery we have preferred to use oral benzodiazepines and, although we would accept that these do not have amnesic properties, have found their sedative and anxiolytic properties to be good. These effects are indeed well recognised.^{1,2}

Although details of perioperative monitoring were not given in our paper, it is in fact our standard practice to monitor patients with an electrocardiograph and automated sphygmomanometer for the reasons so correctly stated by Haylen *et al.* It is interesting to note that the incidence of expulsive haemorrhage may be lower under local than general anaesthesia.³

Patient satisfaction is, as we remarked, difficult to quantify particularly in those who have not previously undergone ocular surgery and therefore have nothing with which to compare. For this reason we did not attempt any formal analysis of it. Only the one patient cited declined surgery to the second eye under local anaesthesia as a day case.

With regard to the provision for management of any emergency, we would reiterate our comment that emergency anaesthetic cover should be available, and this remains a requirement of all our day case lists.

The choice between oral sedation and local anaesthesia and 'assisted local anaesthesia' remains controversial in the United Kingdom, both for ophthalmic and for other surgical procedures, and each unit must choose the appropriate technique to suit local requirements and facilities. We have found success using the technique described, but would not profess it to be the only one suited to day case cataract surgery.

MARK J WATTS
JOHN L PEARCE

- 1 Nimmo WS. Hypnotics, sedatives and anti-depressants. In: Girdwood RM, ed. *Clinical pharmacology*. London: Baillière and Tindall, 1985: 152–3.
- 2 *British National Formulary* 1989; **17**: 429.
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Book reviews

Reap a Destiny: Divagations of a Taoist. By T D V SWINSCOW. Pp. 334. £13.95. British Medical Journal: London, 1989.

Reap a Destiny is a success story but not in the conventional sense. In the dénouement there is no fortune gathered, no presidential appointments recorded, no civic honour flaunted. It is an account of personal adaptation from resentment and self-pity to peace of mind and inner harmony.

'I was about 7 when I realised that my parents often quarrelled over things I knew little or nothing about. . . . I would creep along a corridor, sit on the top stair of the staircase, and listen to their disputes with a lump in my throat and tears welling into my eyes.' At the age of 14 'I began to lose weight. . . and I recall staring into a mirror with a worried expression to see whether any of my hair had turned grey from sorrow.'

In these saddest of sad words lies the nub of the author's inherited problem and they declare the effect of parental strife, openly expressed on a child with an eye for beauty, an ear for music, a mind attuned to poetry, a numerate intellect, and a sensitivity to environmental disequilibrium as responsive as the G string to the bow of the violinist. Such is a prescription for what? A challenge to be faced or not to be faced?

The essential move made by the author to unravel this strangling knot was a process of liberation from the shackles of parental loyalty without irrevocably wounding himself or his parents. This was enacted over a period of lengthy incubation helped by delving into French literature and helped also by communing with Christine Nisbet, a cousin by marriage, a talented artist 10 years older than himself with whom he had fallen in love at a distance. He suddenly appreciated almost by a mystical experience that life on this planet formed a unit of which he was a sharing and significant member and in this concept he found consolation and confidence. At once it put his personal problems into perspective. It became apparent to him that what was denied him in his immediate family was on offer in abundance in the larger family of living organisms. His later researches

strengthened this philosophical outlook, and all his future decisions seem to have been made with reference to this concept.

In his choices throughout life fortune favoured him: in his marriage; in surviving the experience of active service in North Africa, Arnhem, and Norway; in joining the editorial staff of the *British Medical Journal* at a critical time in the development of the National Health Service; in arranging to meet a botanist, Francis Rose, who introduced him to the study of plants in their natural habitat; in his establishment of the British Lichen Society when the Natural History Museum had just appointed a scientist to take charge of its collections; in meeting a kindred spirit in Ursula Duncan; and in accepting an invitation to study the lichens of Uganda and Kenya which resulted in 17 most fruitful years of research recorded in some 30 published papers and gathered together in book form with Hildur Krog as his co-author.

The adventures of these exploits couched in flowing language and punctuated by poetic allusions form the substance of this biography with consummate pen pictures of the co-workers involved. But it would be wrong to think that the author was a passive recipient of these turns of good fortune. 'Fortuna fortes favet' is only part of the whole truth. Persistence of the prepared mind is equally favoured.

Dougal best reveals himself when he writes: 'I delight in the study of natural history because it establishes a sense of kinship with creation. No longer solitary and puzzled, I feel restored to the sea of genes that everywhere casts up living organisms in all their variety of form and function. In analysing their relationships I unconsciously count myself and my friends among them, finding a harmony between us in the matrix of our genetic concordance.'

Only a father of a happy family and a respected member of a close knit community could write in this way. In terms of his own outlook herein possibly lies his crowning achievement. Little wonder that Dougal subscribes to the philosophy of Taoism, the main tenet of which is the unity of all forms of life, a philosophy which appeals to the contemplative and particularly to those for whom the inner life is reality in itself.

STEPHEN MILLER

Vitreous Microsurgery. 2nd Edn. By STEVE CHARLES. Pp. 235. £56.00. Williams and Wilkins: London: 1987.

The second edition of Dr Steve Charles's classic text is an update on his previous work on decision making in vitreo-retinal surgery. The book is aimed at ophthalmologists with an interest (and preferably with a certain amount of experience) in the surgical treatment of retinal disorders.

After outlining the principles of instrumentation in vitreo-retinal surgery the author guides us through the intricacies of various types of operations on the vitreous in both the anterior and the posterior segments. Dr Charles makes use of algorithms to illustrate how to anticipate the various events and complications which may arise during complex vitreoretinal surgery. I find this approach helpful, as it enables the surgeon and the theatre staff to be prepared for,

and to react quickly to, the often sudden changes in the surgical plan.

The book is divided into chapters on a variety of topics such as proliferative vitreo-retinopathy, epimacular proliferation, trauma, and giant retinal tears. I particularly enjoyed the chapters on surgery for proliferative diabetic retinopathy and for the retinopathy of prematurity, subjects in which the author has particular expertise, having pioneered many of the operations described here. The text is illustrated by a few black-and-white photographs, but the book's real strength lies in the many simple but clear line drawings. These are used to emphasise the author's views on the rights and wrongs of various techniques used in vitreoretinal surgery.

The style of the book is somewhat unusual and in places rather authoritative, but those of us who have the privilege of knowing Steve Charles will appreciate his forthright approach to the subject. I have no hesitation in recommending this book to all colleagues interested in vitreo-retinal surgery, and it is a must for all departmental libraries.

Z J GREGOR

Ocular Circulation and Neovascularization: Documenta Ophthalmologica Proceedings Series 50. Eds D BENEZRA, S J RYAN, B M GLASER, R P MURPHY. Pp. 573. £105.00. Kluwer: Dordrecht, Netherlands. 1987.

This volume is a compendium of 88 scientific papers presented at the First Symposium on the Ocular Circulation and Neovascularisation held in Jerusalem, Israel, in September 1986. Dedicated to the memory of Isaac Michaelson, an early pioneer in this field, the book contains a wide range of clinical and basic scientific papers reflecting the interest of morphologists, physiologists, cell biologists, biochemists, and pathologists as well as ophthalmic physicians and surgeons in the ocular circulation and the phenomenon of neovascularisation.

The text is loosely organised into two parts. The first deals with retinal blood flow and vein occlusion, diabetic retinopathy, retinopathy of prematurity, age related macular degeneration, and some aspects of chronic ocular inflammation. The individual papers are wide ranging, with some inevitable overlap of subject matter. The figures and photographs are mostly of good quality, though more stringent editing would have improved the cohesiveness of the text and avoided numerous and unnecessary errors of spelling and syntax and inaccuracies in the reference sections.

The second part of the book is devoted to ocular vasoproliferation in its many forms, with separate sections on neovascularisation of the cornea, the iris, the angle of the eye, and the retina and choroid. A further chapter considers numerous putative angiogenic factors, their origin, nature, and effects on retinal vascular cells in vivo and in vitro. Arguments for the modulating effects of the retinal pigment epithelium on retinal and choroidal vasoproliferation are rehearsed in some detail but as yet without firm conclusion. The concluding section summarises the views of selected investigators in current concepts of ocular neovascularisation.

tion and considers likely areas for profitable future research.

Most of the papers in this volume are informative, well presented, and adequately referenced, though much of the material is often a restatement or summary of work published elsewhere. For the reader not fully conversant with this field there are numerous interesting studies and several concise but valuable review articles, particularly those on laser photocoagulation for diabetic macular oedema and the management of choroidal neovascularisation and corneal neovascularisation.

This book will have particular appeal for ophthalmologists specialising in retinal diseases and also provide useful reading and background data for trainee ophthalmologists or basic scientists wishing to embark on investigative work on the ocular circulation and the many as yet unresolved facets of ocular neovascularisation.

DESMOND B. ARCHER

A Colour Atlas of Allergy. By WILLIAM F JACKSON and RINO CERIO. Pp. 126. £35.00. Wolfe: London, 1988.

This book is the latest in the excellent Wolfe series of simple educational textbooks. Among the wide range of topics covered are basic mechanisms of allergy and investigation of allergic disorders in addition to allergic disorders of the skin, eye, nose, lungs, and gut, and allergic drug reactions. Some chapters describe 'allergy' as just type I hypersensitivity reactions and others incorporate all type I-type IV reactions, which is confusing for the amateur immunologist. Moreover, the inclusion of separate chapters on autoimmune diseases and immunodeficiency syndromes suggest that clinical immunology might have been a more appropriate title.

Professor Easty has contributed the chapter on eye disease. He naturally concentrates, and beautifully illustrates, anterior segment problems, including herpes simplex keratitis because of its increased incidence in atopic subjects.

The hallmark of the book (and the entire series) is the wealth of illustrations and the clarity of the information. After reading the chapter on skin prick tests I thought these were both easy to perform and interpret and perhaps even within the grasp of an ophthalmologist's clinical expertise.

The book includes extensive material covering many clinical specialties all linked by disordered immunity. It is difficult to know who it is aimed at, though undoubtedly all medical students, budding physicians, and curious ophthalmologists would find it both fun and informative.

ELIZABETH GRAHAM

Optic Neuritis. Eds. R F HESS AND G T PLANT. Pp. 310. £35.00. Cambridge University Press: Cambridge, 1986.

The first accurate clinicopathological description of multiple sclerosis in this country came from the pen of a Guy's physician, Dr Moxon, in 1875, and nine years later an eminent St Thomas's ophthalmologist, Nettleship, described the first cases of optic neuritis. In the absence of the diagnostic techniques available today, the group of

patients described was heterogeneous and included cases of ischaemic papillopathy and syphilis, but most of the patients definitely had optic neuritis, presumably due to demyelinating disease. This volume celebrates the centenary of Nettleship's description and is the report of collected papers from a meeting held in November 1984.

The chapters lay great emphasis on the pathophysiology and testing of visual function in optic neuritis, but with minimal consideration of the clinical assessment. Thus the opening chapter by Campbell emphasises the value of contrast sensitivity in normal and abnormal vision. There is an interesting chapter on pathogenesis (McDonald) and one on the neurologist's view of optic neuritis (Herman). The importance of immunological investigation is emphasised (Compston), and this surely will ultimately provide us with an explanation of the cellular events. This is followed by several chapters on the experimental investigation of optic neuritis with psychophysical tests. The experiments on mice have also provided important information and the interesting finding that both fast and slow axonal conduction is accelerated in this condition (Ikeda).

Thus this book provides a useful collection of papers on the scientific investigation of optic neuritis. However, there is little to help an ophthalmologist in the clinic. There is no discussion of colour vision or visual field abnormalities. There is no mention of the great mimic of optic neuritis, the sphenoid sinus mucocoele, and the section on granulomatous optic neuritis is weak. However, the book is worthy of perusal by the clinical ophthalmologist.

M D SANDERS

Notes

European Ophthalmic Pathology Society

The 28th Annual Meeting of the European Ophthalmic Pathology Society was held in Copenhagen (Holte), Denmark on 22–25 May 1989 at the invitation of the Organising Secretary, Professor O A Jensen, assisted by Professor J U Prause, Professor G K Klintworth, of Duke University, Durham U S A and the Verhoeff Society, was the honoured guest. Thirty-two ordinary members of the society also attended the meeting.

The following papers were presented at the scientific meeting: Primary hyperoxaluria (primary oxalosis), (G K Klintworth, U S A). Retinoblastoma in an 'old' patient (K Arnesen, Norway). Conjunctival epibulbar fibrous histiocytoma with orbital extension (E Balestrazzi, Italy). Malignant lymphoma of the brain with vitreous involvement (M Brihaye-van Geertruyden, Belgium). Epithelioma cuniculatum of the eyelid, caruncle and orbit (A Brini, France). Pigmented epiretinal membrane (J G Cunha-Vaz, Portugal). Darier's disease and retinitis pigmentosa (a new oculocutaneous syndrome?) (B Daiker, Switzerland). Juvenile familial amaurotic idiocy (Spielmeier-Vogt) (D de Wolff-Rouendaal, The Netherlands). Macular corneal dystrophy with photophobia (A Garner, U K).

Cholesterolosis bulbi (G Goder, D R). Oil granuloma of the conjunctiva. (R Haedad, Austria). Pseudotuberculosis of the choroid (A Hamburg, The Netherlands). Chondroid syringoma (mixed tumour) of the eyelid? (M Hanssens, Belgium). Ocular toxicity of desferrioxamine (A S Henriquez, Spain). Pigmented neurilemona (schwannoma) of orbit (O A Jensen, Denmark). Gliomeuroma associated with colobomatous dysplasia of the anterior uvea and retina. A tumour simulating medulloepithelioma (T Kivelä, Finland). Adenoid cystic cancer. Interesting postoperative findings (E Kock, Sweden). Retinitis and optical involvement in cytomegalic inclusion disease in a patient with AIDS, who died from cerebral toxoplasmosis (E Landolt, Switzerland). Secondary glaucoma caused by endothelial proliferation 32 years after successful implantation of a Schreck anterior chamber lens (G K Lang F R G). Local recurrence of the iris tumour 24 years after excision (Z Latkovic, Yugoslavia). Successful treatment of a conjunctival melanoma (W R Lee, U K). Retinal lesions after desferrioxamine (J Libert, Belgium). Fetal alcohol syndrome associated with Peters' anomaly (A McCartney, U K). Goblet cell hyperplasia (J Mullaney, Ireland). Oncocytoma of the caruncle (P Naeser, Sweden). Congenital iris cyst (G O H Naumann, F R G). A typical sympathetic uveitis? (M A Parsons, U K). Protracted juvenile neuronal ceroid-lipofuscinosis (J U Prause, Denmark). Myxoid liposarcoma of the orbit (R Proenca, Portugal). Undifferentiated carcinoma from the non-pigmented ciliary epithelium. Metastatic carcinoma? (M Quintana, Spain). Unilateral benign medulloepithelioma associated with bilateral retinal detachment (J Sahel, France). Smooth muscle differentiation of subcapsular cells in anterior subcapsular cataract (A Schmitt-Graff, F R G). Spongy sclera in malignant melanoma of the choroid (F H Stefani, F R G). Histopathology of keratoconus acutus (hydrops corneae). (I Suveges, Hungary). Glaucoma filtering surgery (A Tarkkanen, Finland). A case of rhabdomyosarcoma of the orbit in an infant (H Ueno, Japan). Inflammatory pseudotumor of the orbit (M Vogel, F R G). One type of iridocorneal-endothelial (ICE) syndrome: Cogan Reese syndrome (H E Volcker, F R G). Epibulbar spindle cell tumour (F Weber,

Switzerland). Melanocytic tumour of iris and ciliary body (H Witschel, F R G).

At the business meeting Dr M Sterkers (France) was elected to ordinary membership. The next meeting will be held in Coimbra (Portugal) in June 1990, and Professor J G Cunha-Vaz will act as Organising Secretary.

Cataract surgery

The New Orleans Academy of Ophthalmology will hold its 39th Annual Symposium on Advances in Cataract Surgery on 2-4 March 1990 at the New Orleans Hilton. Further details from: Emily Busby, Executive Secretary, New Orleans Academy of Ophthalmology, 2626 Napoleon Avenue, Room 2076, New Orleans, LA 70115, USA.

Myopia conference

The Fourth International Conference on Myopia, sponsored by the Myopia International Research Foundation, will be held in Singapore on 14-16 March 1990 in conjunction with the XXVI International Congress of Ophthalmology. Further information from: Mrs Sylvia N Rachlin, President, Myopia International Research Foundation Inc, 1265 Broadway, Room 608, New York, NY 10001, USA.

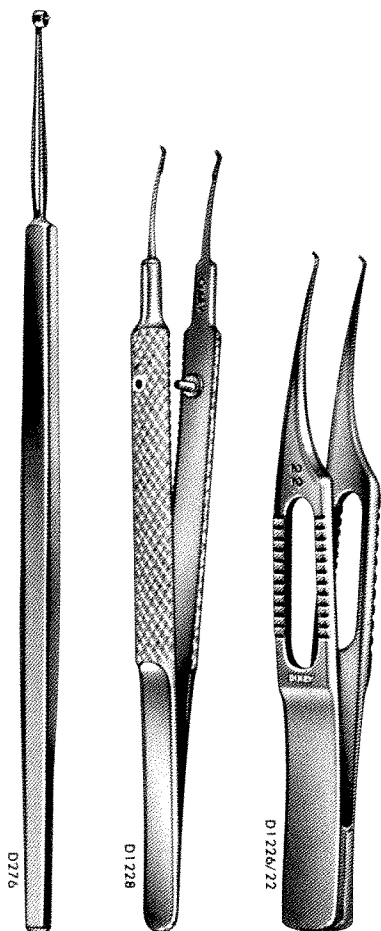
Panhellenic Congress

The 23rd Panhellenic Congress of Ophthalmology will be held on 31 May-3 June at Thessaloniki, Greece. The main themes will be low vision aids, refractive surgery, and cataract and glaucoma. Details from Simeon Lake, MD, PO Box 10497, 54110 Thessaloniki, Greece.

Neuro-ophthalmology symposium

The 8th International Neuro-ophthalmology Symposium will be held at Winchester, England, on 25-29 June 1990. Details from Conference Associates, INOS, Congress House, 55 New Cavendish Street, London W1M 7RE.

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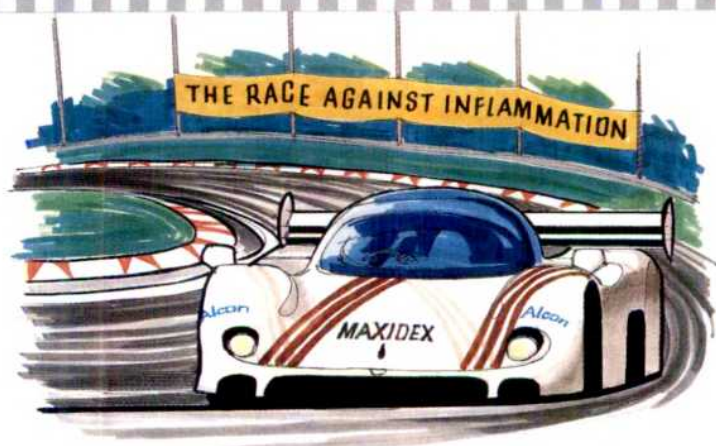
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Editorial: How safe are intraocular lenses?

One of the most important questions from the clinician's (not to mention the patient's) point of view is whether intraocular lenses (IOLs) are more likely to lead to serious complications (and ultimately enucleation) than cataract extraction without implantation. If an extra risk were to be demonstrated, it would then be necessary to put the obvious and unparalleled advantages of IOLs over other methods of correcting the aphakic eye into a 'risk-benefit' equation.

In the absence of epidemiological evidence the solutions of such equations tend to appear gradually, rather as public opinion comes to favour a particular political party, holiday destination, or even brand of sliced bread. However, if one could show that there was no extra risk from a properly performed cataract extraction with an IOL, such concepts as risk-benefit ratios would be irrelevant.

In the article by Professor Garner in this issue the full range of possible complications leading to enucleation in IOL cases is described (and there are in addition valuable histopathological data on successful cases). In 1956, when the previous histopathological report on eyes enucleated following IOL operations was published from the same laboratory as the present study,¹ only a few surgeons were performing the implant operation in the UK, namely, the inventor Harold Ridley and a small band of dedicated pioneers. Most surgeons did not carry out the procedure, at any rate on a significant number of cases, for fear of complications, partly because of unfamiliarity with the technique, which was widely and probably not quite correctly thought to be difficult, but mainly because the method was thought at that time to be inherently dangerous.

An example of what was possibly a widespread opinion at the time was a remark attributed to Paufigue, who had already inserted a considerable number of IOLs. 'We are no longer justified in performing this type of operation because of the too frequent loss of the eye which follows'.² He was certainly not alone in his opinion, and in 1959 the first ominous reports³ were made of keratopathy. This condition was to cast a shadow over the scene for almost another 20 years until the vital role of the endothelium and its terrible vulnerability to 'touch' with the acrylic material became clearly recognised.⁴ Several workers had warned of the dangers of possible endothelial damage previously but without the dramatically convincing evidence provided by

Kaufman and Katz's scanning electron microscopic photographs showing the posterior walls of the corneal endothelial cells literally ripped off and the nuclei lying bare like eggs in egg boxes. None of those who attended that momentous Oxford Congress in 1977 is likely to have forgotten those pictures.

The much improved safety record of modern IOL surgery is based chiefly therefore on the avoidance of endothelial contact, with, as another important subsidiary factor arising out of earlier evidence of damage to the eye by chemical antiseptics used in sterilising the lenses,¹ sterilisation of the lenses by non-chemical means. Professor Garner's paper gives us a salutary reminder, however, that certain complications do still arise, the commonest of which is still keratopathy.

It is an old surgical saying that the only surgeon who gets no complications is the one who does no operations. What we need to know therefore is not the number of complications occurring but the rate, and in the context of IOLs we really ought to know the comparative rates for IOLs versus simple extractions. Clearly an epidemiological study is required, but it is obviously going to be impossible to carry this out on a prospective basis in any of the developed countries of the world because the patients would not tolerate it.

However, public opinion has already taken a hand, and there must be very few ophthalmologists working where the facilities are available, who do not now practice IOL implantation on the majority of their cataract patients. The possibility of extra risk seems largely to be ignored, and indeed it has to be admitted that there is no certain evidence that the total risks are greater. There is even evidence that for some conditions the risks are less, for example that of retinal detachment.⁶

So although the present article by Professor Garner should encourage us to exercise the greatest care in order to avoid complications so far as is possible, it is not likely that significantly fewer IOLs will be implanted as a result of nervousness by surgeons after reading it.

REDMOND SMITH

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Editorial: Importance of early diagnosis in ocular leprosy

The revival of interest in ocular leprosy will prove timely, since the disease now ranks as one of the major contributors to world blindness. Leprosy patients, with their loss of mobility due to the crippling deformities of the disease, should qualify for special consideration in these statistics. Sadly the numbers with severe visual impairment and blindness are unlikely to diminish in the short term despite the widespread introduction of multidrug therapy in the management of the disease.

The ocular complications of leprosy can often be avoided, not only by early diagnosis and rigorous control of the disease and the encouragement of compliance among patients notoriously indifferent to their condition, but also by changing social attitudes to leprosy, which for too long have prevented patients from presenting early in the course of the disease because of the age-old stigma.

Multidrug therapy may well prove effective in reducing the incidence of ocular involvement, provided patients are treated energetically under supervision. Those that slip through the net may develop eye complications which can still be prevented from causing blindness by the constant attention of leprologists, paramedical workers, and the patients themselves.

A word of caution needs to be added at this stage. Evidence is accumulating that some eyes in lepromatous leprosy may harbour living organisms or antigen long after the skin is bacteriologically negative, and ocular disease may recur after patients are released from control. This implies that some form of ocular supervision may need to be continued indefinitely in multibacillary disease irrespective of current practice. The problem of early diagnosis and detection of ocular involvement therefore becomes more

pertinent, and it is here that solid information is lacking at present.

It is known that in early lepromatous leprosy the organisms enter the eye through the blood stream and lodge mainly in the tissues of the ciliary body and iris. Reactions to antigen may occur, giving rise to acute iridocyclitis and obvious clinical symptoms and signs. Frequently, however, the progression of the ocular disease may not be punctuated by acute episodes of inflammation and a slow, relentless, and usually asymptomatic condition occurs, culminating eventually after many years in iris atrophy, miosis, and ciliary body failure. Certain signs may become evident, but they are subtle in the early stages, and by the time they become obvious the eye is irreversibly affected. These signs indicate impairment of autonomic function and include diminished pupil reactions, particularly those involving the dilator muscle, reduced accommodation, and lowered intraocular pressure. None of these can be used singly as a pathognomonic sign of ocular disease, and yet it is of paramount importance to identify those cases with early involvement of the anterior uveal tract, since these may be the patients who run into problems later on.

The paper by Lewallen, Courtright, and Lee in this issue shows that comparisons of intraocular pressure measurements in the upright and supine positions can give useful information about disturbances of autonomic function in the ciliary body with the implication that the tissue has been invaded by *Mycobacterium leprae*. It is to be hoped that this and allied tests can be used to identify those patients at risk, so that they can be singled out for long-term ophthalmic follow-up even after they have been classified as 'cured' by multidrug therapy and released from supervision.

TIMOTHY FFYTCH

Complications of prosthetic intraocular lens implantation: a histopathological study

ALEC GARNER

From the Department of Pathology, Institute of Ophthalmology, University of London

SUMMARY A total of 104 eyes and 43 resected corneal discs from patients with failed intraocular lens implants (IOL) received over a period of 35 years were subjected to histopathological analysis. Eyes collected at necropsy from 18 people with clinically successful implants were also examined. Corneal decompensation leading to bullous keratopathy was the most frequent reason for failure, followed by glaucoma and intraocular inflammation. Of 18 cases in which inflammation was the principal clinical cause of failure 12 presented as infectious endophthalmitis, but minor degrees of sterile uveitis were fairly common. Retinal detachment was seen in seven cases. The interval between IOL implantation and the onset of serious complications varied from one month to 29 years, indicating that the presence of prosthesis will always entail a latent risk of an adverse tissue response, albeit slight.

From rather shaky beginnings the principles and techniques of intraocular lens (IOL) implantation have developed to the level that replacement of the defective lens with a prosthesis is now seen to be the preferred way of dealing with eyes undergoing cataract surgery. Other than in children the limitations on the use of IOLs have more to do with availability and economic restraints than with surgical considerations, and yet there is a significant morbidity associated with their insertion which should not be ignored. Already a substantial number of histopathological reports of the untoward effects of IOLs has been reported and have been well reviewed by Apple and his colleagues.¹ McDonnell, Green, and Champion² identified at least 25 complications in eyes that had undergone apparently successful IOL insertion. The object of the present report is to describe our experience at the Institute of Ophthalmology in the University of London with reference to eyes wherein the prosthetic insertion was mostly unsuccessful.

Materials and methods

Over the period 1953-88 we received 104 eyes from 102 patients and 43 corneal discs (Table 1). Eighteen

of the eyes had undergone successful procedures; all but one of the eyes were obtained post mortem. But the remainder, apart from three eyes which had received implants less than 10 days before death, represented failed implants. Two of the visually successful cases have been reported separately on earlier occasions.^{3,4} The lone eye with a visually successful implant obtained in life was from a patient found to have a malignant melanoma of the choroid some two years later. One hundred and six of the IOLs had been positioned in the anterior chamber (mostly variants of the Choyce and Fyodorov lenses), 14 were iris-clip lenses, and 12 were in the posterior chamber. The available clinical information, particularly in respect of the earlier cases, was inadequate to allow meaningful distinction between cases preceded by intracapsular as opposed to extracapsular cataract extraction.

The specimens were fixed and processed in a conventional manner prior to embedding, sectioning,

Table 1 *Histology of IOL implants 1953-88*

	<i>Successful</i>	<i>Failed</i>	<i>Other</i>	<i>Total</i>
Eyes	18	83	3	104
Corneal discs	0	43	0	43
Total	18	126	3	147
	(12.2%)	(85.7%)	(2.04%)	(100%)

Correspondence to Professor A Garner, Institute of Ophthalmology, 17-25 Cayton Street, London EC1V 9AT.

Table 2 Successful IOL implant procedure

	Histological findings		
	Corneal decompensation	Secondary glaucoma	Anterior uveitis
Anterior (14 eyes)	1	0	4
Iris clip (3 eyes)	0	0	0
Posterior (1 eye)	0	0	0
Total (18 eyes)	1 5.5%	0 0%	4 22.2%

staining, and microscopical examination. In most instances the prostheses were left in situ and dissolved out with chloroform before sectioning, but on some occasions they were removed during the gross examination, with care not to disturb the adjacent tissues more than necessary.

Results

SUCCESSFUL IOL IMPLANTATION

Fourteen of the 18 eyes had received anterior chamber lens implants, three iris-clip lenses, and one a posterior chamber implant (Table 2). Evidence of endothelial cell loss, albeit minor, from the back of the cornea was seen in one eye only in relation to an anterior chamber implant, and there was no associated oedema. In that instance the prosthesis had been in position for three years, and to some extent the loss of endothelium might have been a reflection of the patient's advanced age of 92 years.

Erosion of the iris attributable to the haptics and some fibrous tissue proliferation in the anterior chamber, chiefly in relation to the angles, was observed in most eyes, but it was not of a degree that would have been expected to interfere with aqueous drainage to any significant extent. Posterior iris tucks and minor degrees of angle recession were not uncommon in respect of the anterior chamber implants.

Mild diffuse lymphocytic infiltration of the iris was noted in four eyes.

Table 3 Clinical indications of IOL implant failure

	Bullous keratopathy	Secondary glaucoma	Intraocular inflammation	Other problems
Anterior (92)*	38	32	12	10
Iris clip (12)	10	1	0	1
Posterior (10)	3	1	5	1
Site unknown (12)	9	2	1	0
Total (126)	60 47.6%	36 28.6%	18 14.3%	12 9.5%

*Bracketed figures represent combined numbers of enucleated eyes and resected corneal discs.

Table 4 Histological features of failed IOL implant procedures

	Corneal decompensation	Uveitis	Infectious endophthalmitis	Glaucoma
Anterior (92)*	44	38	8	41
Iris clip (12)	10	1	0	1
Posterior (10)	5	6	3	3
Site unknown (12)	9	3	1	2
Total (126)	68 54.0%	48 38.1%	12 9.5%	47 37.3%

*Bracketed figures represent combined numbers of enucleated eyes and resected corneal discs. Infectious endophthalmitis cases are listed as a subdivision of the total uveitis group.

FAILED IOL IMPLANTATION

The clinical reasons for failure with the corresponding histopathological findings are listed in Tables 3 and 4. In most cases these took the form of bullous keratopathy, glaucoma, or intraocular inflammation, but in a few cases such diverse problems as postimplantation trauma, stromal keratitis, and corneal abscess leading to perforation were implicated.

BULLOUS KERATOPATHY

Bullous keratopathy was the commonest clinical cause of failure (Fig. 1), presenting in 60 of the 126 cases (47.6%). So far as could be ascertained from histological examination, there was no evidence of an

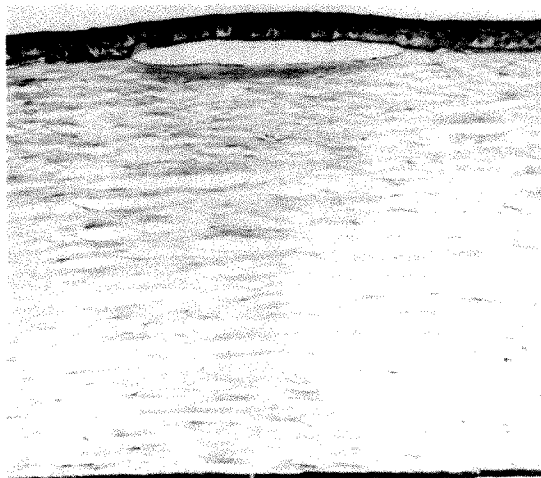


Fig. 1 Bullous keratopathy secondary to an anterior chamber IOL implant. The corneal endothelium is abnormally sparse. (Periodic acid Schiff and haematoxylin, $\times 100$).

alternative explanation, such as Fuch's dystrophy, for the corneal oedema, though in five specimens (four related to anterior and one to posterior chamber implants) there were signs of concurrent stromal inflammation. Four of the resected corneas were associated with retrocorneal membranes (three anterior chamber prostheses and one of unknown placement). Clearly enucleation would not be entertained for isolated corneal disturbance, but in several instances this was a major component of the patients' complaints in conjunction with such lesions as anterior chamber fibrosis and glaucoma. Thus some 18 enucleation specimens were reported to have bullous keratopathy on clinical grounds, while histological examination revealed significant endothelial cell atrophy and loss in 28 of the 83 eyes, giving a combined incidence of corneal decompensation for eyeballs and resected corneal discs of 55.6%.

GLAUCOMA

Secondary closed angle was the next most frequent complication in the unsuccessful implant procedures, being the principal problem in 36 of the 126 cases (28.6%). However, histological inspection indicated that there was evidence of choroidoretinal atrophy and cupping of the optic nerve head consistent with clinically raised intraocular pressure in another 11 eyes, to give an overall incidence of 37.3%. One of the most frequent underlying tissue changes was extensive fibrosis within the anterior chamber (Figs. 2 and 3), often appearing to have derived from the cornea and rarely enveloping the IOL to form a pseudocapsule. A second common finding was of corneoid adhesions, which were sometimes

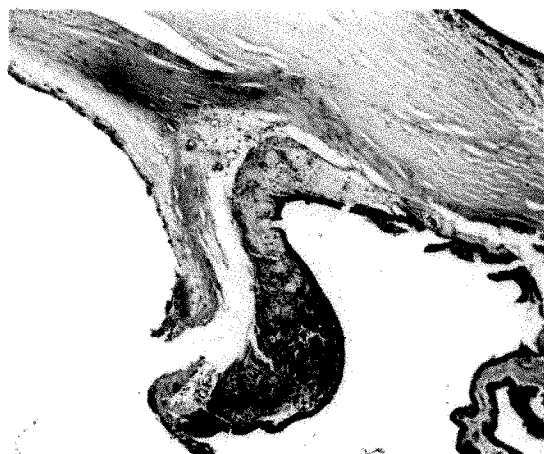


Fig. 2 Dense, partly vascularised, retrocorneal fibrous tissue obliterating the filtration angle in response to an anterior chamber IOL inserted five years earlier. There is also posterior tucking of the iris. (H and E, $\times 26$).



Fig. 3 The anteriorly located IOL is surrounded by fibrous tissue which appears to have emanated from the cornea at the site of the lensotomy scar. A fibrous membrane is also present on the surface of the iris, and there is a retinal detachment. (H and E, $\times 26$).

associated with rubeosis iridis in the presence of chronic retinal detachment. Occasionally interference with aqueous outflow was attributable to epithelialisation (five cases) (Fig. 4) and, exceptionally, to descemetisation (one case) of the anterior chamber. In some instances, particularly where there had been repeated surgical intervention, it was not possible to determine the basis of the glaucoma.

INFLAMMATION

Clinically diagnosed endophthalmitis, occurring

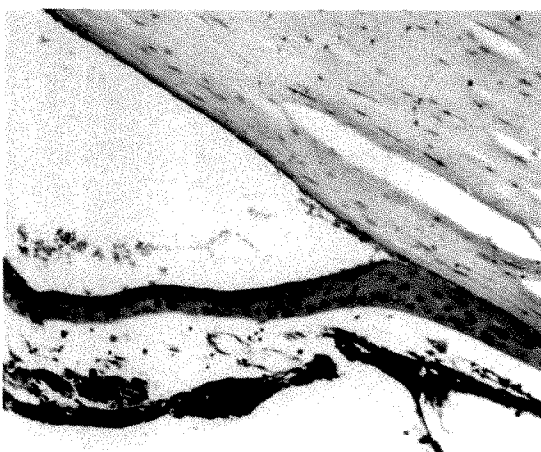


Fig. 4 Squamous epithelium is covering the surface of the iris and occluding the filtration angle secondary to an anterior chamber IOL introduced two years before. (H and E, $\times 110$).

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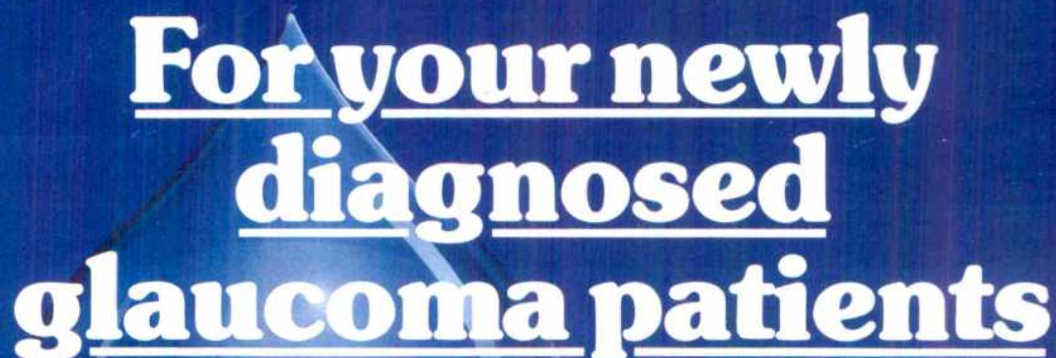
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Kitazawa, Y. et al. Acta XXIV International Congress of Ophthalmology, 1983; P. Henkind (Ed.), Lippincott, Philadelphia.

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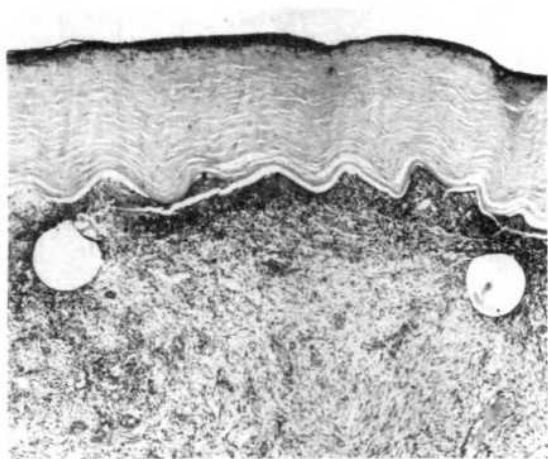


Fig. 5 Endophthalmitis with partially organised purulent exudate filling the anterior chamber and surrounding the haptics of an anterior IOL present for two months. (H and E, $\times 26$).

between six days and 46 months after IOL implantation, was the reason for enucleation in 12 instances (Fig. 5). Bacterial infection was implicated in all but one patient, from whom a fungus was isolated; in that instance infection with *Trichosporon beigelii* developed nine months after insertion of an anterior chamber IOL. Minor degrees of anterior uveitis, chiefly in the form of diffuse lymphocytic infiltration of the iris, were identified in a further 36 eyes. Presumed non-infective uveitis was the presenting clinical problem in six other patients, raising

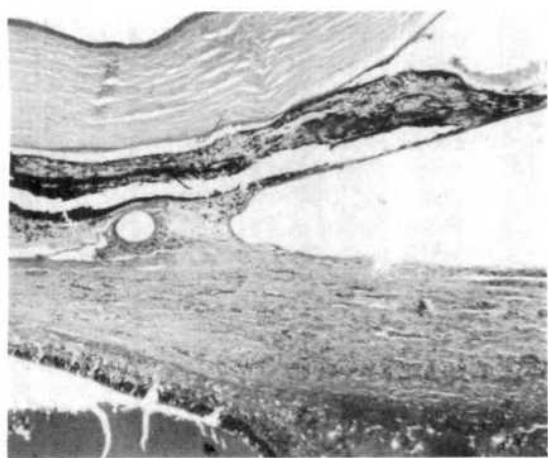


Fig. 6 Retinal detachment in the presence of a fibrovascular cyclitic membrane and a posterior chamber IOL. There is also forward displacement of the iris and an extremely shallow anterior chamber. (H and E, $\times 26$).

suspicions of impending sympathetic ophthalmitis in one. Altogether intraocular inflammation of all grades of severity was noted histologically in 48 eyes but only in 18 (14.3% of the series overall and 37.5% of the globes with demonstrable uveitis) was it the presenting condition.

RETINAL DETACHMENT

Total or subtotal detachment of the retina was observed in seven eyes (Fig. 6). Five of them had had anterior chamber and two of them posterior chamber implants.

Discussion

DURATION OF IMPLANTS

The length of time between insertion of the IOLs and examination of the eyeballs in patients with wholly successful implants varied widely from two months to 17 years (average 3 years 8 months), while, where the information was available, the interval in those with failed procedures ranged between one month and 25 years (average 5 years 5 months). In a number of instances the IOL was removed some time before enucleation, and in these cases it is the shorter period that has been used for the analysis. The extremely long spells that can be experienced before the situation deteriorates to the level where surgical intervention is required begs the question as to what constitutes a successful IOL procedure: an eye which has tolerated an implant for upwards of 10 years prior to serious complications (14 of the 95 ostensible failures in which the time interval was stated) ought to be accorded at least a measure of success. In nine of those 14 there was evidence of endothelial decompensation. On the other hand it would seem that at no stage is there freedom from the risk that problems will arise.

CORNEAL DECOMPENSATION

Corneal oedema, associated with subepithelial bullae and subsequent fine fibrosis and pannus formation, appears to have a variety of causes in the context of IOL complications. The corneal endothelium may be physically damaged at the time of implantation or subsequently through contact with the implant, especially in relation to prostheses sited in the anterior chamber.⁶ Physical abrasion of the iris, particularly where the prosthesis has rough or sharp edges, may also be a factor by provoking a sterile inflammatory reaction. However, the finding that only six of the 26 globes (23.1%) from patients with implant failures involving endothelial decompensation presented an associated chronic uveitis, compared with 27 of the 78 specimens (34.6%) in which there was no corneal disturbance, does not

suggest that inflammatory factors are of prime importance in causing endothelial damage. (The concurrence of stromal keratitis in a few instances would not normally be expected to interfere with endothelial function.) Epithelialisation and descemetisation of the anterior chamber were less common factors, as was retrocorneal fibrosis, but the contribution of raised intraocular pressure in the patients with concomitant glaucoma is not to be disregarded (15 of the 26 glaucomatous globes showing endothelial cell inadequacy).

But, whatever the reason, bullous keratopathy was the commonest type of failure following IOL insertion, and, as in the experience of Champion and Green,⁷ penetrating keratoplasty was the most frequent form of surgical intervention. The data are insufficient to show any differential susceptibility to corneal problems between the separate varieties of IOL.

SECONDARY GLAUCOMA

The overall incidence of glaucoma in patients receiving IOLs has been estimated to vary between 0.7 and 4.3% and is the second most frequent complication in terms of requiring further surgery.⁷ Documented causes include occlusion of the filtration angle by peripheral anterior synechiae⁸ or more extensive anterior segment fibrosis,⁹ by descemetisation, or by epithelialisation of the anterior chamber consequent on the lensectomy.² The first of these possibilities was commonest in the present series, the iridocorneal adhesion being due in turn to inflammation, presumed trauma attributable to the haptics of the prosthesis, or retinal detachment and secondary rubeosis iridis. However, appreciable degrees of anterior segment abnormality of the type outlined can be observed in clinically successful implants,² indicating that it is the extent of involvement that is important. Angle recession also appeared to be a significant factor in persons receiving anterior chamber IOLs. Pigment dispersion is a common finding, even in cases with good visual results, so that, while it may conceivably contribute to aqueous outflow restriction, it is unlikely to be a major factor in provoking glaucoma. The presence of an IOL does not of itself appear to cause a significant rise in intraocular pressure.¹⁰

INFLAMMATION

Suppurative endophthalmitis affected 12 of the eyes with failed implants, and in four cases in which it developed within the first three months infection introduced at the time of surgery may reasonably be blamed. Contamination of the neutralising solutions used in the days of wet-pack sterilisation by both bacteria and fungi has been incriminated in some

reports.^{7,11,12} In those patients in whom the post-surgical interval varied between nine months and almost four years it would seem more likely that the infection was endogenous. In such an event the infection may have been facilitated by foci of tissue damage and necrosis induced by the implant.

Minor degrees of anterior uveitis are not uncommon, even in respect of successful implants – four of 18 eyes in the present study and 29.6% in an examination of 203 eyes by McDonnell *et al.*² Nevertheless, over half (56.4%) of the 85 globes with unsuccessful IOLs showed either iritis and/or cyclitis, and in six cases sterile uveitis refractory to anti-inflammatory medication was the main reason for undertaking enucleation.

Reported causes of persistent uveitis include mechanical irritation, toxicity of the solutions bathing the prosthesis prior to insertion,⁹ allergic reactions to residual lens material in the case of extracapsular cataract extractions, and immunological disturbances involving complement.¹ There is evidence that complement can be activated directly by the prosthesis through the alternative pathway.¹³

A syndrome of uveitis with hyphaema and secondary glaucoma has been described, particularly in relation to anterior chamber IOLs, in which the initiating factor is considered to be physical damage as a result of instability or roughness of the implant.¹⁴ Sterile uveitis associated with glaucoma occurred in 23 eyes in the present study, of which 20 were anterior chamber implants, two posterior chamber implants, and one an iris-clip implant, but the available clinical information does not allow a statement on the concurrence of hyphaema.

RETINAL DETACHMENT

The reported incidence of retinal detachment in pseudophakic individuals is between 0.2% and 2.4% according to a recent review,² which compares favourably with the 0.8% to 4.9% incidence given for cataract extraction without IOL implantation. The same authors recorded four cases in their survey of 203 eyes that had largely acceptable visual results, and the present finding of seven instances of retinal detachment in an overall series of 147 specimens, most of them from unsuccessful procedures, is probably not excessive. Apple *et al.*¹ note that, while IOL implantation does not seem to be a significant aetiological factor in detachment, it can reduce the chances of successful surgery should the retina become detached for some other reason.

CONCLUSION

The success rate for intraocular lens implant procedures has increased enormously in recent years. Most of the failures in the present study related to anterior

chamber implants (93 out of 127), but then so did the successes (14 out of 18), and it is not possible from these data to assess the relative merits of the various implant procedures.

Minor degrees of uveitis and of anterior chamber distortion appear to be compatible with clinical success, though the extremely late onset of complications in a substantial number of the patients suggests that there will always be some risk of eventual failure. This does not constitute an argument against IOL surgery, however, since it may take a lifetime (or longer!) for serious problems to arise.

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Ocular autonomic dysfunction and intraocular pressure in leprosy

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SUMMARY We examined 241 leprosy patients and 135 age-matched healthy controls in central South Korea, measuring intraocular pressure in the supine and the upright positions and measuring the size of the pupils in darkness as an indication of ocular autonomic dysfunction. The mean intraocular pressure was significantly lower in the patients and the mean size of pupils was significantly smaller in the patients than in the controls. However, there was no correlation between pupil size and intraocular pressure in our patients. Our findings show that leprosy patients have ocular autonomic dysfunction, but do not support previous speculation that this dysfunction is the primary cause for low intraocular pressure in leprosy.

Leprosy is a disease which affects 10–12 million people in the world.¹ There are wide variations in reports of the prevalence of ocular complications from it.² Differences in race, type of disease, duration of disease, and reporting methodology may all be responsible for this variation. There are several ways in which the leprosy bacillus affects the eye. Lagophthalmos, superficial and interstitial keratitis, corneal nerve beading, and nodules on the sclera and cornea are manifestations of bacillary infiltration of nerves and anterior segment structures. Acute iridocyclitis may occur, but more frequent is a unique chronic iridocyclitis. In this condition the eye is white and quiet, with the gradual development of severe miosis. Posterior synechiae may develop as well as complicated cataracts.

Low intraocular pressure has been reported in leprosy patients in several studies.^{3,4} Furthermore, it has been reported that some leprosy patients show significant postural changes in intraocular pressure and suggested that this might be due to loss of autonomic function in the anterior segment of the eye, presumably due to bacillary infiltration of the ciliary nerves.⁵

We examined leprosy patients and healthy controls in a racially homogeneous population, looking for ocular pathology and measuring the intraocular

pressure in the upright and supine positions. As a measure of ocular autonomic dysfunction we measured the size of the pupils in complete darkness. Size of the pupil in the dark has been shown to be a reliable measure of ocular autonomic dysfunction in diabetics.⁶ We present our findings in this paper.

Materials and methods

As part of a programme to train leprosy paramedical workers to recognise potentially blinding disease in leprosy patients all patients (n=605) in eight leprosy resettlement villages in Kyeong Buk province, South Korea, were encouraged to undergo an ophthalmic examination. Of these patients 509 (83%) were examined.

In small villages all examined patients were included in the intraocular pressure and pupil studies. In larger villages, for logistic reasons, a systematic sample of half the patients was selected for intraocular pressure and pupil study. Voluntary controls, known to be free of leprosy, were obtained from the outpatient department of the Catholic Skin Clinic and Hospital in Daegu. Controls were matched for age to the patient population. All subjects with diabetes and eyes with previous intraocular surgery or trauma were excluded.

Visual acuity was tested by a trained health worker. A sticker with an identification number was

Correspondence to Dr Gordon J Johnson, Director, International Centre for Eye Health.

Table 1 Intraocular pressure and postural change in pressure in eyes of healthy controls and leprosy patients

	Right eye			Left eye		
	Controls	Patients	<i>p</i>	Controls	Patients	<i>p</i>
Intraocular pressure (mm Hg), mean with SD (no)	14.2 (2.9) (120)	13.6 (3.2) (218)	0.05	14.2 (2.9) (121)	13.1 (3.3) (216)	0.01
Postural change in pressure (mm Hg), mean with SD (no)	1.4 (2.2) (118)	1.8 (2.8) (215)	0.15	1.2 (1.9) (119)	1.6 (2.3) (210)	0.06

placed on the forehead between the eyebrows, and the patient was positioned against a head rest connected to the camera lens (28 mm macro) and ring flash. A photograph of the patient's pupils was taken with 100 ASA slide film. With the patient in exactly the same position a darkness hood made of absolutely light-proof fabric was placed over the patient. The hood enclosed the camera lens and headrest and was designed to drape over the shoulders of the patient and exclude all light. After 20 seconds in complete darkness another photograph was taken. The patient was then examined by an ophthalmologist with a portable slit-lamp. Next the patient had one drop of fluorescein instilled in each eye and the intraocular pressure was measured in first the right, then the left eye with a Perkins applanation tonometer. The patient assumed the supine position and the intraocular pressure was immediately measured again, right eye then left eye.

The above procedure was followed on both patients and controls except that no visual acuity testing was done on controls. The slides of pupils were projected at a magnification of approximately 5 $\times$, and the size of the pupils and the identification sticker in each slide was measured. An independent examiner read 10% of the slides to check agreement. Exact magnification of each slide was calculated from known and magnified sticker size and the true pupil diameter in mm calculated for each eye. All eyes with posterior synechiae were excluded when we analysed dark pupil size, since mechanical restriction of the pupil in these eyes would invalidate pupil size as a measure of autonomic dysfunction.

Relationships among variables (upright and supine intraocular pressure, pupil diameter, signs of ocular pathology, and age) were established for individual eyes by means of multiple regression analysis, Pearson's correlation coefficient (*r*), and analysis of variance. To avoid problems caused by intracorrela-

tion between right and left eye in an individual, we report results for left and right eyes separately.⁷

Results

We enrolled 241 leprosy patients in our study: 181 (75%) had multibacillary disease and 53 (22%) had paucibacillary disease. The remainder were of unknown disease classification. The age range was 28–76, mean 53 years. The mean duration of disease was 33 years. We enrolled 135 controls of similar age.

There was a significant difference between leprosy patients and healthy controls in intraocular pressures (Table 1). Furthermore, eyes of leprosy patients with posterior synechiae had a mean intraocular pressure of 12.6 mm Hg compared with 13.5 mm Hg in eyes of leprosy patients without synechiae (*p*=0.03). There was no association between age or disease type and intraocular pressure. The mean postural change in intraocular pressure was greater in patients than in controls but this difference was not statistically significant (Table 1).

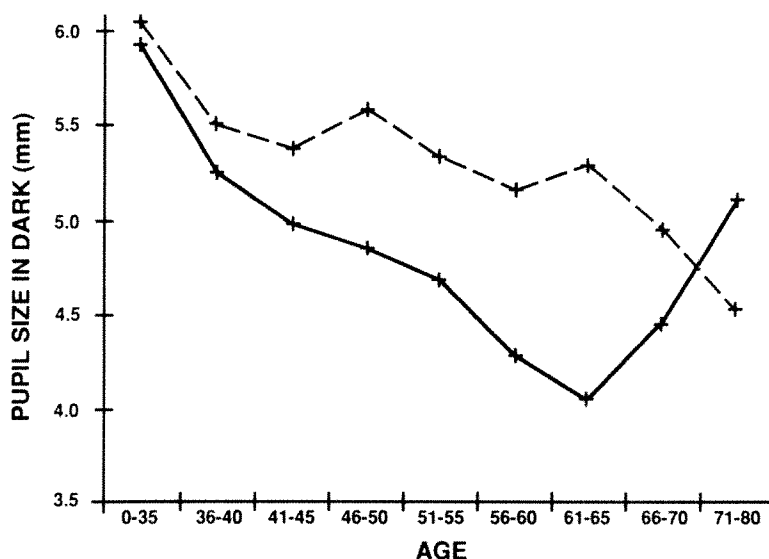
The mean pupil size of leprosy patients was smaller than that of healthy controls (Table 2). In both leprosy patients and healthy controls size of pupils in the dark was age dependent. This dependence is shown in Fig. 1. (Since the left and right pupils are essentially the same size they have been combined in this figure.) Pupil size was not associated with disease type. There were few patients in the oldest age groups, resulting in increased variability of pupil size in these groups.

Among the patients' eyes there was a negative correlation (right eye *r*=−0.149, left eye *r*=−0.117) between intraocular pressure and postural changes in pressure (*p*>0.05). There was no association between either intraocular pressure or postural change in intraocular pressure and pupil size in the dark.

Table 2 Pupil size in the dark in eyes of healthy controls and leprosy patients

	Right eye			Left eye		
	Controls	Patients	<i>p</i>	Controls	Patients	<i>p</i>
Pupil size (mm), mean with SD (no)	5.3 (0.07) (115)	4.8 (1.1) (182)	0.001	5.4 (0.7) (117)	4.6 (1.3) (185)	0.001

Fig. 1 Pupil size in the dark in leprosy patients (solid line) and healthy controls (broken line).



In the control group there was a positive correlation (right eye $r=0.237$, left eye $r=0.267$) between intraocular pressure and pupil size in the dark ($p<0.01$). There was no correlation between intraocular pressure and postural change in pressure.

Discussion

Our findings of intraocular pressure in leprosy patients confirm those of others—that is, pressures are lower in this group of patients than in the general population. We also demonstrate that leprosy patients show significant ocular autonomic dysfunction compared with normal controls. However, in our patients we did not find any association between ocular autonomic dysfunction and intraocular pressures or postural changes in intraocular pressure.

The mechanism by which the ocular autonomic system influences intraocular pressure is not well understood. We can only speculate as to the cause of lower intraocular pressure in leprosy patients. If these pressures were due only to ocular autonomic dysfunction, we would expect to find a correlation between dark pupil size and intraocular pressure in our patients, which we did not find. It was interesting that we did find such a correlation in our control group, in which decreasing sympathetic tone was associated with decreasing intraocular pressure independently of age.

Low intraocular pressures in leprosy could be due to damage to the ciliary body secondary to chronic low grade iridocyclitis. Ffytche has suggested that the chronic iridocyclitis seen in multibacillary patients may be gradual atrophy of the dilator muscle (pre-

sumably due to ocular sympathetic nerve dysfunction) rather than a true inflammatory process.⁸ Our findings support this theory in that we found that eyes of leprosy patients do not dilate normally in the dark in comparison with controls and that these eyes were white and quiet with no cells in the anterior chamber. In our study and others,⁹ leprosy patients with posterior synechiae have intraocular pressures significantly lower than patients without synechiae. However, our method of testing for autonomic dysfunction cannot be used in eyes with posterior synechiae, so it is not clear what the relative contributions of chronic iridocyclitis and ocular autonomic dysfunction to low intraocular pressure in leprosy might be.

As in a previous study,⁹ we found a negative correlation between intraocular pressure and postural change in pressure in our leprosy population; however this was not statistically significant in our study. The mechanisms controlling the homeostasis of intraocular pressure with change in body position are not clear. There are reports that patients with open angle glaucoma, low tension glaucoma, ocular hypertension, systemic hypertension, and diabetes show large postural changes in intraocular pressure compared with normal persons.¹⁰⁻¹² This phenomenon is thought to be related to vasomotor dysfunction. However, we found no association between postural change in intraocular pressure and ocular autonomic dysfunction.

It is desirable to find a method of detecting patients at risk for chronic iridocyclitis early in the disease before vision is impaired. Our findings do not suggest that intraocular pressure measurements will be help-

ful in doing this. However, our leprosy patients all had a long disease duration. It is possible that control mechanisms which the autonomic system normally exerts over intraocular pressure may be severely altered in patients with long-standing disease. Longitudinal analysis of intraocular pressure in newly diagnosed patients will aid our understanding of this.

Studies of ocular autonomic function and intraocular pressure in leprosy patients will help clarify the ocular pathophysiology of this disease. Furthermore, studies of intraocular pressure in patients with ocular autonomic dysfunction may help to explain the role of the ocular autonomic nervous system in intraocular pressure regulation in healthy eyes.

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The demand incidence of cataract in Asian immigrants to Britain and their descendants

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SUMMARY Cataract is known to be more common in India than it is in the industrialised world, but there is little evidence to show whether people emigrating from India will continue to have a high incidence of the disease. Data have been collected from the outpatient clinics of a hospital in Leicester, England, that suggest that for people aged over 45 the demand incidence of cataract is more than five times higher in people of Indian descent than it is in the indigenous population. As well as measuring the demand incidence of cataract in Leicester's two main racial groups the data are used to investigate other risk factors. For both communities the demand incidence of cataract is significantly higher in women than in men, and it is significantly higher in people of Indian descent who emigrated directly from India than in those who emigrated from East Africa. Religious subgroups within the immigrant community also show small differences in their demand incidence. The possibility that these differences are linked to diet is considered.

It has frequently been observed that senile cataract is more common in developing countries than it is in industrialised countries. The Indian subcontinent has been reported as having an especially high prevalence of cataract,¹⁻⁴ with one study in the Punjab¹ finding a prevalence that varied with age between three and six times that found in the Framingham Eye Study.^{5,6}

It is not at all clear why senile cataract should be more common in India than it is in industrialised countries. However, large epidemiological studies of eye disease and reviews of the risk factors for cataract do give us some clues.⁵⁻⁹ Among the risk factors that have been investigated are sex,¹⁰ a family history of the disease,¹¹ diet,^{3,12} environmental factors, particularly sunlight,¹³⁻¹⁵ socioeconomic factors such as poor education,⁶ and medical conditions including diabetes,⁹ and previous severe diarrhoea.¹⁷ It has also been suggested that some of the observed differences between populations may be due to differences in study methodology and definitions.⁸

A high rate of cataract among people of Indian descent is of particular interest in Britain because in the 1950s, 1960s, and 1970s large numbers of Indians

came to live in this country. At first they came mainly from the Indian subcontinent itself, but later many descendants of Indian families came to Britain after being expelled from their adopted countries in East Africa. Leicester is one of the cities where the immigrants chose to settle, and they now constitute about a quarter of the city's population.

Material and methods

The Leicester Royal Infirmary is the centre for eye care for the whole county of Leicestershire, and the ophthalmology department has recently been engaged in a major workload survey of its outpatient clinics.¹⁸ The survey started on 1 September 1981, and results from the first two and a half years of data collection have been used as the basis for measurements of the demand incidence of cataract, that is, the number of new cases of cataract presenting at the hospital per 100 000 population per year. The survey included everyone seen at the outpatient clinics during the time of the study. The data collected on each patient included their age, sex, the postcode of their address, their ethnic origin, country of birth, religion, and whether or not this was their first outpatient eye appointment. The survey also took

the ophthalmologist's diagnoses and coded them according to the 9th revision of the International Classification of Diseases.¹⁹

To calculate demand incidence rates information is needed on the population structure of the catchment area of the hospital. As the Royal Infirmary is the centre for ophthalmology in Leicestershire, all cases of cataract among people resident in the county should in theory be seen there. However, there will be some loss of cases round the edge of the region when people choose to travel to other centres such as Derby, Nottingham, or Coventry. The Indian community of Leicestershire is largely confined to the City of Leicester, and very few people from any ethnic group who live in the city are likely to travel out of the region for eye care.

The structure of the population of the City of Leicester was studied in detail in a 16% household survey carried out in the spring of 1983 at the request of the City and County Councils.²⁰ To make use of the detailed information available on the city's population and to avoid problems of loss of cases across the boundaries of the county the analysis presented below has been restricted to persons living within the city. Everyone who visited the outpatient clinic was classified on the basis of their postcode to decide whether or not they should be included in the analysis.

The outpatient clinic studied in the workload survey is intended for the treatment of adults, though children aged under 16 are occasionally seen. To avoid problems associated with partial coverage and because juvenile cataract probably has a different aetiology from age related cataract, persons under the age of 16 were excluded.

The demand incidence rates were calculated by dividing the number of new cases of cataract, obtained from the hospital survey, by the appropriate population estimates as obtained from the household survey. The rates have been analysed and adjusted for age by means of a method of indirect standardisation,^{21,22} with the calculations performed with GLIM.²³

Results

Table 1 shows the average demand incidence rates obtained in the study. Without any adjustments for age the rates are seen to be generally higher in women than men and in people of Indian rather than Caucasian descent. Age specific rates are given in Table 2 and the variation with age is illustrated by Fig. 1. This plot shows that the average demand incidence of cataract increases steadily with age in all groups, and confirms that the rates are consistently higher in women and in Indians. When indirect standardisation is used to smooth these data, Fig. 2 is

Table 1 The number of cases and demand incidence for Leicester residents by race and sex. Numbers relate to the period September 1981 to March 1984

		Number	Demand Incidence per 100 000 per year
Caucasian	Male	151	76
	Female	261	116
Asian	Male	79	146
	Female	84	159

Table 2 Age specific demand incidence rates by race and sex

Age	Average demand incidence per 100 000 per year			
	Caucasian		Asian	
	Male	Female	Male	Female
16-29	6	2	12	4
30-44	7	13	18	6
45-59	67	14	212	291
60-64	88	114	803	1098
65-69	252	243	746	1810
70-74	283	361	2170	1897
75-79	350	631	1963	1159
80+	333	524	3571	1482

obtained, together with the age adjusted relative rates given in Table 3. Averaged across all age groups the demand incidence of cataract is significantly higher in Indians than Caucasians ($p < 0.0001$). Men

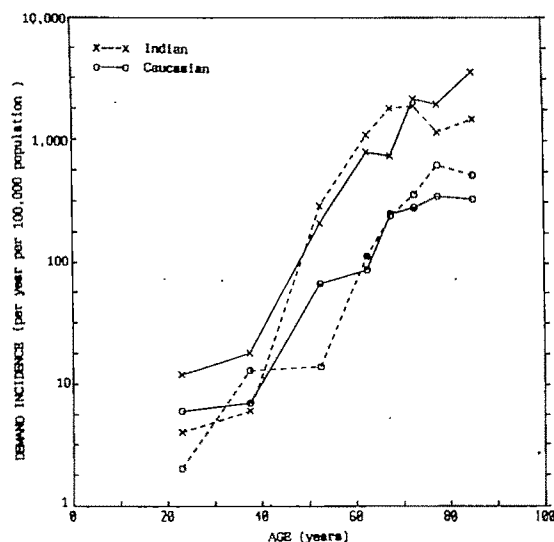


Fig. 1 The observed age specific demand incidence rates for Indians and Caucasians. Males: solid line. Females: broken line.

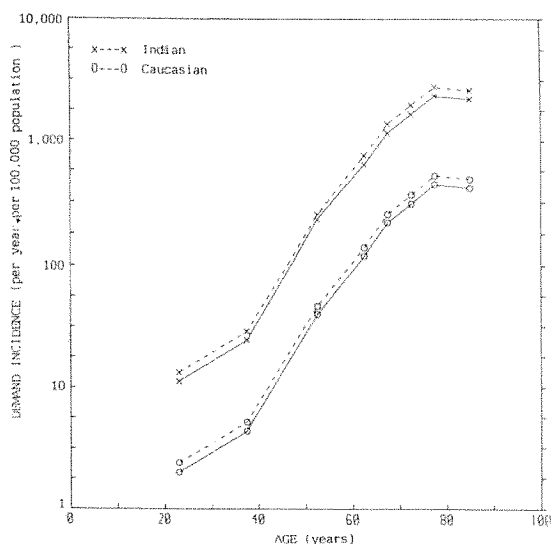


Fig. 2 The smoothed age specific demand incidence rates for Indians and Caucasians. Males: solid line. Females: broken line.

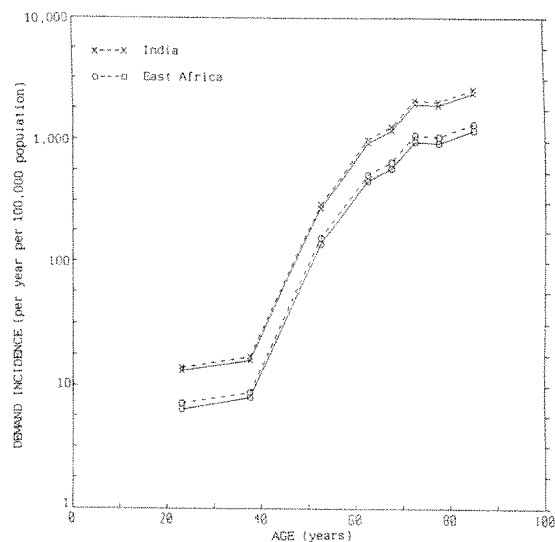


Fig. 3 The smoothed age demand incidence rates for Indian immigrants from India and from East Africa. Males: solid line. Females: broken line.

and women show the same relative rate due to race, estimated at 5.4 with a 95% confidence interval of (4.4, 6.5). The rate for women is about 20% higher in both racial groups, a difference that just reaches conventional significance levels ($p=0.05$).

Although the relative rate averaged across all age groups is estimated as 5.4, there is evidence of a significant difference in the relative rate between people aged under 45 and those aged 45 and over ($p=0.004$). For people under 45 the estimated demand incidence rate for cataract is estimated to be 1.6 times higher in Indian immigrants than in the Caucasian population. This difference is not significant. In contrast, for people aged 45 and over the relative rate is estimated as 5.7, a highly significant difference ($p=0.0001$).

Fig. 3 shows the smoothed rates for those immigrants who came directly from the Indian subcontinent as compared with those who came from East Africa. The corresponding age adjusted demand incidence rates for cataract are given in Table 4. The rates are significantly higher in those who came from India ($p=0.001$). The relative rate is the same for

men and women and is estimated at 2.1 with a 95% confidence interval of (1.1, 3.9).

The division of the demand incidence rates by religious subgroup (Table 5, Fig. 4) is significant ($p<0.0001$), but the difference is due to the contrast between Indians and Caucasians. The difference between Hindus and the other Indian groups is not significant ($p=0.13$).

Discussion

The use of existing sources of data is a common method of epidemiological investigation and an important stage in the planning of more rigorous surveys. However, such studies are often subject to

Table 4 Age adjusted relative demand incidence rates of cataract for Asians by region of birth and sex

	Male	Female
East Africa	1.0	1.1
India	2.1	2.2

Table 3 Age adjusted relative demand incidence rates of cataract by race and sex

	Male	Female
Caucasian	1.0	1.2
Asian	5.4	6.3

Table 5 Age adjusted relative rates of cataract by racial subgroup and sex

	Male	Female
Caucasian	1.0	1.2
Asian: Hindu	5.6	6.9
Sikh or Moslem	4.8	4.6

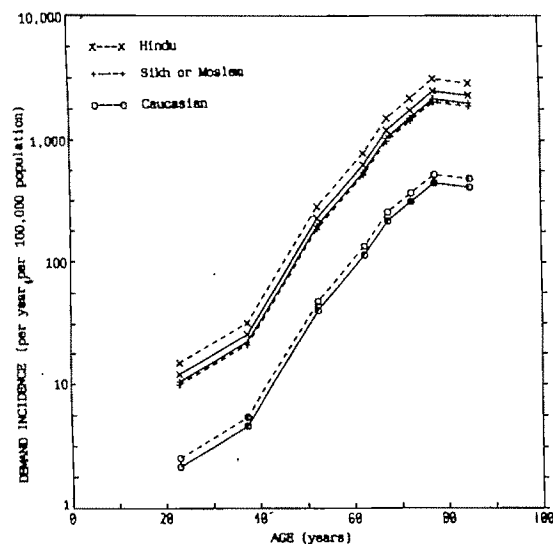


Fig. 4 The smoothed age specific demand incidence rates for Caucasians, Hindus, and Sikhs and Moslems combined. Males: solid line. Females: broken line.

bias, and in this particular study it was necessary to consider whether the outpatient clinics saw all potential cataracts, whether the diagnoses are reliable, and whether the population figures are accurate.

In order to ensure as complete a coverage as possible the target population used for the study was defined as adults resident within the city boundaries. Treatment of Leicester residents by other centres is unlikely to be a problem, but a number of people do opt for private treatment and would then not be seen at the outpatient clinics. A survey in the neighbouring city of Coventry worked with an estimated rate of 5% private treatment.²⁴ Such a rate, even if disproportionately divided between the Indian and white communities, would be insufficient to explain the differences found in this study.

The outpatient clinics were run by a number of different ophthalmologists over the two and a half years of the study, and there may have been differences in their diagnosis of cataract. The little research that has been conducted^{25,26} shows a good agreement between ophthalmologists in the detection of signs of cataract, and consequently variation in diagnosis may not be a major problem.

The effect of using population estimates has been studied elsewhere.²⁷ Provided the population estimates are not biased, their effect will be to increase the variability associated with the estimates of relative risk with only small impact on the sizes of the relative risks.

Bearing in mind the limitations of the data, we

must judge the epidemiological significance of this study with care, but we believe that the data give us a true overall picture. The demand incidence found in Leicester and the variation with age are both very similar to those found in Coventry in 1972.²⁴

The results of this study show a relative demand incidence for cataract between Asians and Caucasians that is very much in line with the relative rates observed in separate studies in India and in industrialised countries. It would appear, therefore, that the previously reported differences derived from separate studies are not due to methodological effects, differences in definition, or inequalities in the standard of health care available at the time of diagnosis.

The significantly lower relative rates in people aged under 45 years is encouraging, because it may reflect the early benefits of improved health care and better standard of living experienced by the Indian immigrants. However, the possibility that the aetiology of cataract may be different for young adults requires that the relative rates be followed up carefully over the coming decades.

The difference in rate observed between people from India and people from East Africa may be due to the nature of the immigration of the two groups. People came to Britain from India to achieve a better standard of living, whereas those from East Africa were mostly expelled for political reasons. As a consequence those from India tend to be from lower socioeconomic groups, while the East Africans are a cross-section of society.²⁸ The difference in rates of cataract would be consistent with a social class gradient, perhaps indicating better diet and health care.

The difference between Hindus and other Indian religious groups is not significant ($p=0.13$), but this comparison lacks power and a difference cannot be discounted. As Table 6 shows, vegetarianism is much more common in Hindus, and we agree with other investigators that this is a risk factor that deserves further study. Lack of protein in the diet was identified as a risk factor for cataract in one Indian study,³ and vegetarianism in Indian immigrants to Britain has been suggested as an explanation for below average growth rates in children²⁹ and high rates of ischaemic heart disease.³⁰

Table 6 The percentage of Leicester residents in each racial group who do not eat meat

Caucasian	1%
Asian: Hindu	34%
Sikh	9%
Moslem	9%

Although they could not be allowed for in this analysis, there is good evidence to suggest that diabetes, cardiovascular disease, and high blood pressure are all general risk factors for cataract.^{5,7,9,16}

A number of studies have noted the increased prevalence of diabetes in Indians,³¹⁻³³ and it is likely that this is a factor contributing towards the increased rate of cataract.

The results of this study highlight the impact of immigration on the workload of the ophthalmic services in Leicester. They also indicate a number of risk factors that are worthy of further study. These factors are being investigated in a community survey of eye disease in Leicester.

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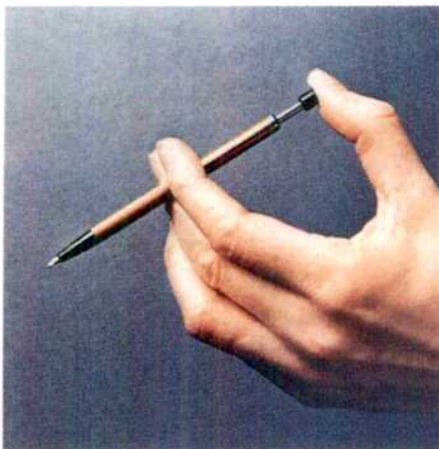
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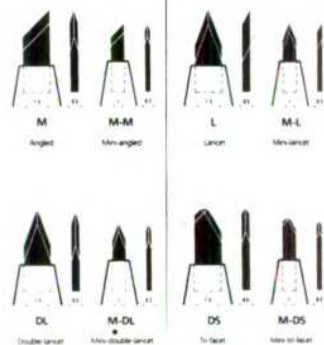
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Relationship of cataract to radiation sensitivity

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SUMMARY Considerable exposure to radiation always causes posterior subcapsular cataract (PSC). This investigation was conducted to ascertain whether cellular hypersensitivity to radiation may be identified as a possible cause of cataract in persons exposed to low levels of radiation. Patients were studied in whom PSC had followed probable exposure to low levels of radiation or in whom PSC had developed before the age of 60 without known exposure. The patients with cataract were compared with age and sex matched controls without cataract. Radiation sensitivity was estimated by measuring clonal growth of skin fibroblasts and peripheral blood lymphocytes after exposure to graded doses of radiation and by measuring postirradiation reconstruction of separated nuclear material from lymphocytes. The results show variations in the level of radiation sensitivity between the patients, without significant differences from the controls. It is concluded that radiation hypersensitivity, as tested by the methods used in this study, is not normally associated with the development of posterior subcapsular cataract.

The lens of the eye is unusual in that it grows at a steady rate throughout life¹⁻³ by mitosis of the germinal epithelium at the lens equator and the formation of new fibre cells on the surface of the lens cortex. Cessation of growth is observed in cataract, particularly in subcapsular cataract.^{1,4,5}

The morphology of cataract developing in the adult is divisible clinically into three major categories: cortical, nuclear, and subcapsular. It is probable that the mechanism of cataract formation is different in each of these three categories, with the common end result of increased light scattering in the lens. Biochemical research into mechanisms of cataract formation has been intensive and a large volume of knowledge now exists.⁶ This information relates largely to cortical and nuclear cataract, with less known about subcapsular cataract.

Spontaneous posterior subcapsular cataract (PSC) is described as senile, or presenile, according to the age of the patient. Alternatively PSC may be second-

ary to other eye disease, such as uveitis,⁷ retinal detachment,⁸ and other retinal diseases. In these cases it is described as complicated cataract. Other causes are metabolic disease and drug induction by corticosteroids.^{9,10}

A significant external cause of PSC is ionising radiation by x rays¹¹ and by neutron radiation.^{12,13} Chronic exposure to low x ray dosage has also been implicated.¹⁴ Absorbed radionuclides are another possible cause.¹⁵ PSC occurring 'naturally' and those cases induced by radiation have a very similar clinical morphology (Figs. 1 and 2) and are also histologically similar.^{4,10,14,16} It appears that the primary defect is in the germinal epithelium, which fails to undergo normal mitosis to produce new lens fibres and instead produces granular material, which is seen as cataract and is observed histologically in the subcapsular region.

Thus failure of mitosis can account for both the histology and for the cessation of growth of the lenses developing PSC. In the case of radiation induced cataract it is reasonable to assume that these changes occur because of damage to the DNA of the germinal

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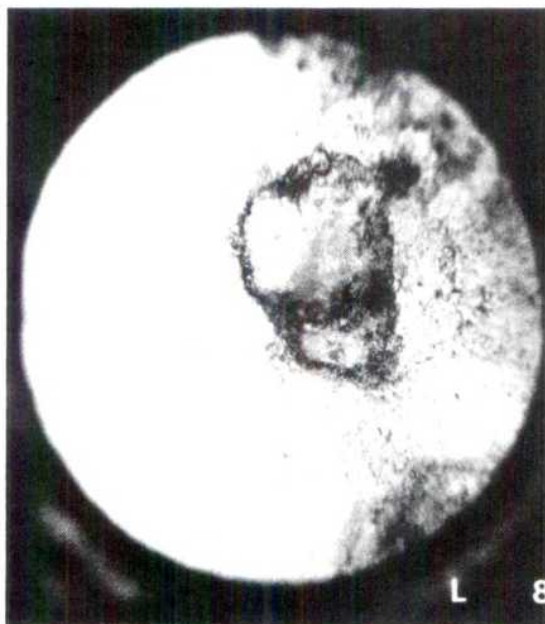


Fig. 1 Posterior subcapsular cataract in one of the Christmas Island personnel photographed on the Oxford retroillumination camera.

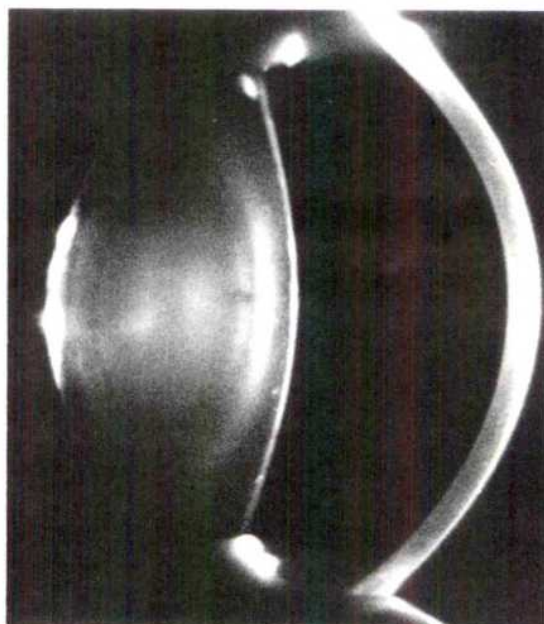


Fig. 2 The same eye as in Fig. 1 photographed on a slit-image camera.

epithelium of the lens. In those cases of PSC occurring 'naturally' it is possible that there has been a mutagenic change in DNA affecting mitosis and/or protein synthesis. The cause of this change is obscure, but it could conceivably have occurred as a result of abnormal sensitivity of the individual to radiation. The radiation responsible may have been either normal background radiation, or other exposure to low doses of radiation that would not normally be considered cataractogenic.¹⁷

Complicated cataracts are probably different in origin and have a different histology: capsular permeability being implicated in uveitis⁷ and subcapsular fibroplasia in retinal detachment.⁸ The mechanism of drug induced cataract by corticosteroids is suggested to be due to binding of the drug to the protein of the lens fibre.¹⁸

The individual variation in susceptibility of cancer patients to skin damage during radiation treatment is known to be considerable. Occasionally such susceptibility is so profound as to interfere with a course of treatment. It was such a clinical observation that led to the recognition of extreme cellular sensitivity to x rays, implying defective DNA repair, in ataxia-telangiectasia.¹⁹ Studies on fibroblasts from 'normal' individuals, entailing the construction of dose-survival curves, have shown statistically signifi-

cant differences of almost 100% between Do^* values for least and most sensitive persons.^{20,21} Individual variation to x ray induced DNA damage can thus be determined. An abnormally low (highly radiosensitive) Do value has been shown in patients with severe normal tissue reactions to therapeutic radiation.²²

To test the theory that naturally occurring subcapsular cataract might be related to abnormal radiation sensitivity we set out to examine the cellular radiosensitivity of patients with subcapsular cataract of no known cause and in those patients in whom it was suggested that subcapsular cataract had occurred as a result of exposure to small doses of radiation. This latter group of patients included all those personnel known to us who had attended the Christmas Island atomic weapon testing in the 1950s and who had subsequently developed cataract before the age of 60. It had been suggested that the prevalence of cataract in these personnel was greater than should be expected and that the cataract might

*The expected survival was calculated as:

$$\log S_{exp} = \log [c \{1 - (1 - e^{D/Do})^n\}]$$

where D is the gamma radiation dose, Do is the reciprocal of the slope, and n the extrapolation number. The term c is included so that the expected surviving fraction is not constrained to 100% at zero dose.

be the result of radiation received in Christmas Island.

Materials and methods

OPHTHALMIC

The patients were divided into three groups.

Group A. Christmas Island veterans (16 patients) known from our records of a previous study, or notified to us by the Christmas Island Veterans Association, who were thought to have cataracts, were invited to partake in the study.

Group B. Presenile PSC (11 patients) who were attending the Oxford Eye Hospital and had pure PSC of no identifiable aetiology. Of these, five had worked in environments where they might have been exposed to low levels of radiation.

Group C. Controls (six subjects) were chosen from an age matched population of fit healthy male volunteers with no past history of significant medical or ophthalmic complaints. Any control with any degree of cataract or an anterior clear zone not equal to grade 3 was rejected.

For the better understanding of the results the Christmas Island veterans were further subdivided into three groups. Group 1A (six patients) were those who were found on examination to have PSC (two patients), or aphakes (four patients), who had been noted by an ophthalmologist in the past to have PSC. Group 1B (six patients) were those who on examination did not have PSC. One of these patients was a unilateral aphake in whom the type of cataract previous to surgery was unknown. Group 1C (four patients) were those who had had cataract extractions, but in whom the type of cataract was unknown.

All patients and controls gave informed consent to the study.

OPHTHALMIC EXAMINATION

A full medical and ophthalmic history was obtained with particular reference to exposure to radiation. In the past history we specifically asked about all factors that are known to be associated with the causation, or with the avoidance of cataract²³: diabetes, renal or hepatic failure, hypertension, and carcinoma or leukaemia. The use of alcohol or tobacco or of any medication, especially steroids, analgesics, diuretics, nifedipine, and allopurinol, was inquired about. Patients were asked about eye injuries and ophthalmic surgery or medication taken. All patients were refracted, and the visual acuity was recorded by the Log MAR Ferris chart. Pupils were dilated with G phenylephrine 10% and G tropicamide 1%, repeated at least once in order to achieve a pupil size of 8 mm. In addition to a full ophthalmic examination the lenses were graded by the same observer using the

Oxford Clinical Cataract Classification System.²⁴ The lenses were also photographed with the Brown slit-image camera and the Oxford retroillumination camera.²⁵ Blood for a random blood sugar was taken, and a further 60 ml of blood was taken and placed in heparin without preservatives. A small 3×3 mm sample of skin from the patient's forearm was taken under local anaesthetic. Blood samples and skin biopsies were then examined in a coded fashion within 24 hours.

RADIATION SENSITIVITY

The radiation sensitivity of lymphocyte DNA was tested at the Hammersmith Hospital by the method of buoyant density centrifugation as already described.²⁷⁻²⁸ The radiation sensitivity by clonal assay for cell survival was measured at the MRC Cell Mutation Unit by means of skin derived fibroblasts^{29,30} and T lymphocytes.³¹

Results

Table 1 shows the results in the controls and patients who were examined, with a brief description of the type of cataract or of other eye disease that was found.

There were 16 patients who had been present at Christmas Island. Of these PSC was found in two at the time of examination and believed from the hospital records to have been present in four others, making six cases in all. There were three others with cataract of unknown type, making it possible that there were a total of nine cases of PSC.

The history was not significant in suggesting alternative causes for cataract.

Eleven patients were examined who had not been to Christmas Island and had PSC. Of these, five had possible exposure to radiation at work.

The percentage number of hypersensitive samples of lymphocytes, as tested by buoyant density centrifugation at the Hammersmith Hospital, for all the individuals in the present study was 16, that is, intermediate between those in the other two studies^{27,28} tested by the same methods. The mean age in the present study, 53.8, was intermediate between the mean ages of the individuals in the previous two studies of 38.6 (5% hypersensitive population²⁷) and 79.7 (26% hypersensitive population²⁸), thus showing a relationship with age but not with subcapsular cataract.

The data on radiation sensitivity, as measured in lymphocytes by buoyant density centrifugation and in fibroblasts and T lymphocytes by clonal assay, was analysed by the statistical package GLIM (Royal Statistical Society, London). No patient with PSC was found to be hypersensitive to radiation when the

Table 1 *Relation of cataract to radiation sensitivity*

	Age	%Repair	Lympho Do	Fibro Do	R eye	L eye
<i>Group 1A Christmas Island with posterior subcapsular cataracts</i>						
01	63	0	1.44	1.62	PSC	(?)
01	51	69.5	1.30	1.68	(PSC)	(PSC)
03	50	61.4	1.62	1.50	(PSC)	(PSC)
04	54	100	1.71		(PSC)	(PSC)
05	49	60.9	1.59	1.58	Clear	(PSC)
06	52	36.8	1.51	1.51	(PSC)	PSC
<i>Group 1B Christmas Island without posterior subcapsular</i>						
07	63	50	1.77	1.43	N Brun	N Brun
08	51	85.7	1.55		Spoke	Spoke
09	50	51.3	1.52	1.48	ASC	(?)
10	49	59.5	1.60	1.69	Mature	Spoke
11	50	12	1.95		Focal dot	Ret. Detach.
12	55	27.3	1.59	1.57	Clear	Clear
13	50			1.15	Clear	Clear
<i>Group 1C Christmas Island with cataract of unknown type</i>						
14	53	0	1.42	1.67	Clear	(?)
15	52	63.8	1.42		(Mature)	clear
16	51	53	1.32	1.33	(?)	(?)
<i>Group B Non-Christmas Island with posterior subcapsular cataract</i>						
17	50	76.5	1.55	1.15		
18	60	70.4	1.47	1.21		
19	62	64.8	1.50			
20	54	20	1.21	1.67		
21	53	44.4		1.44		
22	58	100	1.22	1.28		
23	32	67.7	1.61	1.35		
24	56	82.4	1.49			
25	51		2.40			
26	58		1.28	1.51		
27	39		1.82	1.40		
<i>Group C Normal controls</i>						
28	52	59.1	1.92	1.56		
29	50	53	1.38			
30	52	62.2		1.36		
31	56	55.2	1.27	1.19		
32	54	59.1	1.07	1.36		
33	49	64.8	1.76			

% Repair = % lymphocyte DNA repair after irradiation tested at the Hammersmith Hospital.

Lympho (fibro) Do = Survival of lymphocyte (fibroblast) cell culture (Gy); as tested at the MRC Cell Mutation Unit.

Parentheses indicate an aphakic eye—that is, (PSC) means an aphakic eye which had a PSC according to notes available, which may be misleading in certain cases. (?) Means aphake with no record of type of cataract.

ASC = anterior subcapsular cataract. PSC = posterior subcapsular cataract. N Brun = nuclear brunescence. Spoke = spoke cataract.

results were compared with those from the study controls. In addition, in the clonal assays the results were compared with those from concurrent laboratory controls used in every experiment, and again no significant differences were observed. The observations on clonal survival will be reported in detail elsewhere.

Discussion

Approximately 18 000 personnel were present at the UK atmospheric nuclear weapon test programme at Christmas Island between 1952 and 1967, and of these 1000 are believed to have died, leaving 17 000 remaining.³² In these tests radioactive material was dispersed into the atmosphere, and they were followed by a clean-up operation. Attention was drawn to an apparent excess incidence of cancer in this group³³ (this has subsequently not been confirmed³⁴). It appeared from information reaching us at Oxford that there might also be an excess incidence of cataract in this group, since we had information before beginning our present study of 26 cases believed to be of PSC, being 0.15% of the sample of 17 000. Our present study shows that we have knowledge of only 12 cases of cataract (an incidence of 0.07%), and of these only six are of the PSC type that might be attributed to radiation. The mean age at examination of these cataract cases is 57 years, which falls into the age range in which cataract is uncommon. The frequency of cataract extraction for males in the age range of 40–49 in Oxford is 0.003% rising to 0.023% at ages 50–59.³⁴ These figures relate to cataract extraction, and the prevalence of early cataract is necessarily higher than this. Senile cataract was reported in 3.5% of persons under the age of 65.³⁵ Thus the incidence of cataract now known in the Christmas Island personnel of 0.07% is not more than expected. There will be cases that have not been brought to our attention, but there is no evidence that the incidence of cataract in the Christmas Island personnel exceeds the normal.

Subcapsular cataract is the least common of the three major types of cataract (cortical, nuclear, and subcapsular), and the stated proportion of cataracts that are subcapsular varies widely in different series, being reported as 6%,³⁶ 10%,³⁷ 24%,³⁸ 40%,³⁹ and 50%³⁵ in western studies and as only 1% in the Punjab.⁴⁰ These figures are for patients of all ages, and the proportion of PSC may be higher in younger people.³⁸ Thus the proportion of PSC in the Christmas Island personnel, being 50% of those known to have cataract, is an expected value, and the minimum overall prevalence of PSC at 0.04% of the Christmas Island personnel fits within the reported range. There is therefore no indication of any excess prevalence of subcapsular cataract that would indicate a radiational cause in the Christmas Island personnel.

Radiation sensitivity testing by the three methods now reported showed inconsistent results between the systems. The Do values for cell killing obtained by means of skin derived fibroblasts or T lymphocytes obtained from blood samples showed no significant differences between the groups of individuals tested.

The postirradiation repair of lymphocyte DNA did show marked differences between individuals, but the occurrence of a low figure for repair was unrelated to the development of subcapsular cataract.

CONCLUSION

Radiation sensitivity, as tested by the methods used in this study, is unrelated to the development of cataract.

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Primary optic nerve sheath meningioma

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SUMMARY Fifty patients with optic nerve sheath meningiomas have been reviewed with a follow-up of up to 15 years. The median age at onset of their symptoms was 40.0 years. The majority were middle aged females with a slowly progressive lesion. More aggressive lesions were encountered in a younger, predominantly male group of patients with frequent intracranial involvement. Our experience indicates that a more aggressive surgical approach to these lesions is needed to prevent this sequence of events. Meningiomas in older individuals often do not need treatment, though radiotherapy can be beneficial.

Meningiomas within the orbit may arise from the meninges of the intraorbital optic nerve (primary optic nerve sheath meningioma) or from the meninges of the optic canal or sphenoid bone. Very rarely orbital meningiomas appear to arise from ectopic arachnoid cells separate from any meningeal tissue. This paper deals with meningiomas primary to the optic nerve sheath. In the past we treated these by local excision. In the older patients there have been few recurrences, but it has become increasingly apparent that the younger the patient the more aggressive the growth and spread of the meningioma. Our management of these patients has therefore changed. This paper details our experience and our suggested treatment in patients of differing age.

Patients and methods

The diagnosis of optic nerve sheath meningioma has been made in 50 patients from a total of over 3000 seen in the Orbital Clinic at Moorfields Eye Hospital. Histological confirmation has been obtained in 44 cases. The remaining six have not undergone surgery, and the diagnosis has been made on the basis of typical clinical and radiological features. The presence of good vision has been the major reason for not operating on these patients, but in a few patients old age and general medical problems have influenced the decision.

In many patients it was not clear at the time of presentation, even with sophisticated methods of investigation, whether the meningioma had arisen

within the orbital optic nerve sheaths (primary optic nerve sheath meningioma) or from the meninges of the optic canal or adjacent sphenoid bone. However, we have included only patients who clinically presented as if their meningioma was primarily affecting the optic nerve sheath and excluded those who quite clearly had meningiomas of the sphenoid which secondarily affected the optic nerve. In the group reported on here it is quite probable that some of the meningiomas were not primary to the optic nerve sheaths in the strictest sense, but such a distinction is, we believe, both unhelpful and unnecessary, as the decisions to be made about the patient's management are essentially the same.

In all cases a detailed clinical history was obtained and a full ocular and neurological examination performed. Routine skull films with optic canal views were always obtained. All but a few patients have undergone CT scanning, and a small number have also had angiography and magnetic resonance imaging (MRI).

Thirteen patients have been referred for craniotomy, the oldest of these being 52 at the time of surgery. Orbitotomy, usually via a lateral approach, has been performed in all other operated cases and also on many of the craniotomy patients. In those undergoing orbital surgery and attempted excision our initial approach involved stripping the nerve sheath and meningioma from the underlying nerve in the hope of preserving vision. In all these cases the eye was rendered blind as a result of the surgery and there was a high incidence of extradural orbital recurrence. In a small number an attempt to preserve vision was made by slitting open the nerve sheath to

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Table 1 Age and sex data

Total patients	50		
Sex	Male 17	Female 33	
Involved optic nerve	Right 20	Left 30	
Age at onset	Mean	Median	Range
All patients	38.9	40.0	5-65
Males	33.3	30.0	5-61
Females	43.2	42.0	12-65
Age at presentation			
All patients	43.2	40.0	10-70
Males	38.5	31.0	10-78
Females	47.2	46.0	20-66

decompress the nerve. In these patients meningioma recurred in the orbital fat and extraocular muscles. We now aim to remove the nerve and its sheath en bloc, whether this be via a craniotomy or an orbitotomy or a combination of the two.

Results

The age and sex distributions of the patients are presented in Table 1 and the age at onset of symptoms is shown graphically in Fig. 1. The males were clustered in the younger age group, so that of those whose symptoms began before the age of 20 years five out of six were male. Of all 13 patients aged 30 and under 10 were male, and of those 27 patients aged 40 or less 12 were male. This compares with the overall sex ratio of 17 males to 33 females. This increased number of males was statistically significant for the groups aged 20 or less and 30 or less (χ^2 test with Yates's correction gives $p < 0.025$ and $p < 0.001$ respectively), but not for those aged 40 or less ($p > 0.1$).

The presenting symptoms and their duration are detailed in Table 2. Most patients noticed loss of vision as their first symptom, and this often preceded the recognition of any proptosis by a year or more. Of

Table 2 Presenting symptoms

Symptom	Number	Duration (years)		
		Mean	Median	Range
Visual loss	45	4.8	3.0	0.2-28
Proptosis	18	3.3	2.0	0.1-10
Obscurements	7	0.5	0.2	0.1-1.5
Diplopia	3			
Lid swelling	3			
Pain	2			

the patients with visual obscurations one had these as his only symptom. In three patients the obscurations were gaze evoked, occurring in abduction. In two they were brought on by postural changes, and in the remaining two they were spontaneous. The vascular basis of these obscurations was proved in one patient by fluorescein angiography.¹ On abduction of the globe the central retinal arterial flow ceased and then returned as the eye resumed the primary position.

The clinical findings at presentation are outlined in Table 3. Almost one-third of patients (16/50) had 6/18 or better vision when first seen. The amount of proptosis was generally small (median 2.0 mm) and did not correlate closely with the visual acuity, though all patients with 6/6 vision had 2.0 mm or less proptosis (whereas those with no perception of light ranged from 0 to 8 mm).

The majority of patients had an atrophic optic disc, and, in about a third of these, opticociliary shunt vessels were present. The patient with a normal disc had 6/6 vision. His meningioma was discovered incidentally on CT scan for a suspected acoustic neuroma; no surgery has been performed. This patient does not have neurofibromatosis. In the whole series only one patient did, and he had the central form of the condition with bilateral acoustic neuromas (Case 1 below).

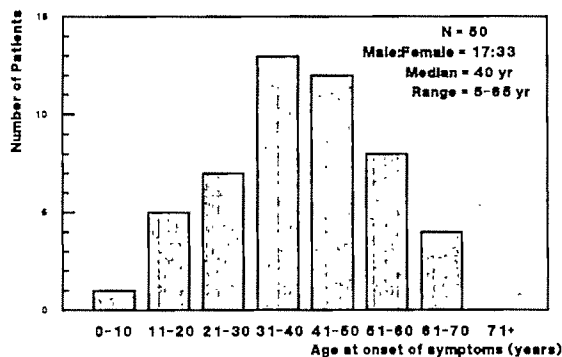


Fig. 1 Age at onset of symptoms for 50 patients with optic nerve sheath meningiomas.

Table 3 Clinical findings at presentation

Visual acuity	Number	(%)
6/6-6/9	10	(20)
6/12-6/18	6	(12)
6/24-6/36	4	(8)
6/60-Count fingers	8	(16)
Hand movements-light perception	10	(20)
No light perception	12	(24)
Proptosis	Mean	3.3 mm
	Median	2.0 mm
	Range	0-11 mm
Optic disc	Atrophic	31
	Swollen	19
	Opticociliary shunts	12
	Normal	1

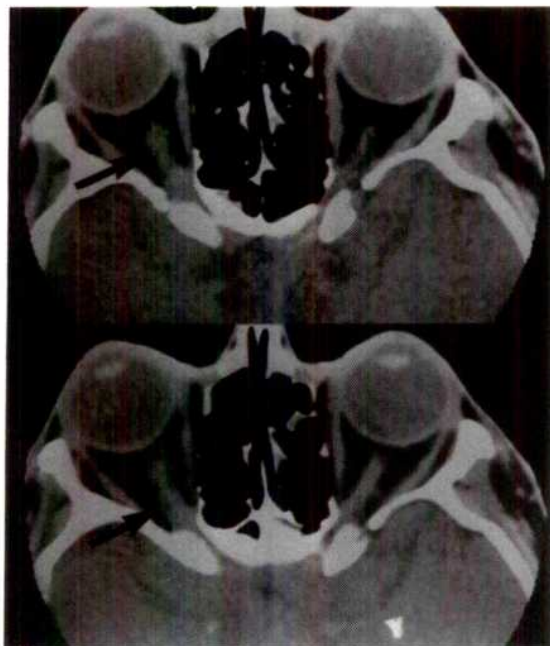


Fig. 2 Axial CT scan with contrast of a patient with diffuse enlargement of the optic nerve caused by meningioma (arrowed).

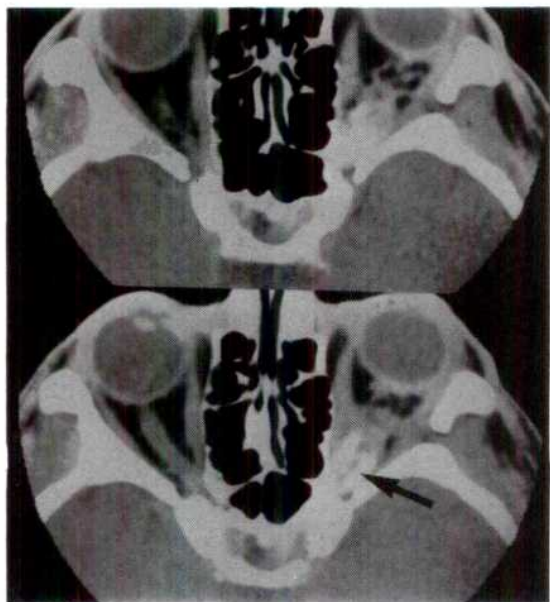


Fig. 3 Axial CT scan with contrast showing 'tramline' calcification within the sheath of the optic nerve (arrowed). This elderly patient previously had a lateral orbitotomy and excision of the anterior two-thirds of the orbital optic nerve and its sheath.

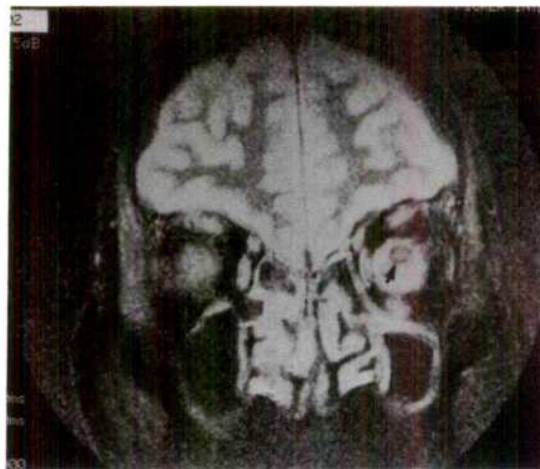


Fig. 4 Coronal MRI showing a meningioma surrounding the optic nerve (arrowed).

CT scans (Fig. 2) were performed in 47 cases. Ten patients showed definite calcification of either a 'tramline' type (Fig. 3) or scattered within the tumour on CT scan. Of the 31 cases with histopathological confirmation in whom a CT scan was performed prior to surgery and the radiologist's report was available a confident diagnosis of meningioma was made in 23. This gives a diagnostic accuracy rate of 74%. Ten of these showed calcification. In four the radiologist was equivocal, reporting the presence of an optic nerve tumour only. In four the diagnosis was incorrect. Three were reported as likely to be glioma. All three of these patients were young at the time of the scan (ages 10, 20, and 20 years). One patient in whom the expansion of the optic nerve was reported as meningioma was found to have cystic expansion of the optic nerve sheath. An apical meningioma not seen on the original scan was discovered only several years later. These scans were performed on equipment ranging from the prototype scanner of 1972 up to current, high resolution machines. In patients seen and scanned since 1980 the diagnostic accuracy has been over 90%.

Table 4 Intracranial disease related to the age of onset of symptoms

Age at onset of symptoms	Intracranial disease detected by CT or MRI	Total with intracranial disease
20 years or less	3/6	4/6
21-30	2/7	2/7
31-40	5/13	7/13
41-50	3/12	3/12
51-60	1/8	1/8
61+	0/4	0/4

MRI was used in only a small number of cases (Fig. 4), and its value in the assessment of optic nerve meningioma is still under review.

No patients had symptoms or signs of intracranial disease at presentation or within the course of follow-up. However 13 had radiological evidence of intracranial disease on CT. One further patient had intracranial disease detected only on MRI. Three patients without radiological evidence of intracranial disease were found at craniotomy to have a small amount of meningiomatous tissue emerging from the proximal end of the optic canal. One of these had had MRI in addition to CT.

There were 14 patients with radiological evidence of intracranial involvement. In addition three were found to have intracranial spread only at craniotomy, CT scans having failed to detect it. We excluded these three from the following statistical analysis, as we have tended to recommend craniotomy only for the younger patients, and this introduces a bias. Of the 14 with radiologically detected intracranial disease 10 were 40 years or less at the time of onset of their symptoms. This does not represent a statistically significant age related difference (χ^2 test with Yates's correction gives $p < 0.25$). If this trend were to continue, between 2 and 3 times as many patients would be required to attain statistical significance. For patients aged 20 or less, three out of six developed intracranial disease detected with CT scan, and one other was found to have intracranial spread at craniotomy. The incidence of intracranial disease in all age groups is represented in Table 4. Five were male and 12 female, but this difference is not statistically significant. In addition there was no difference in the types of investigation performed in the different age groups, and the period of follow-up was similar in each group.

Prior surgery did not have a significant effect on the development of intracranial disease. Of the 17 patients with intracranial disease 10 had had no previous surgery. Three had a small biopsy via an orbitotomy 2, 7, and 8 years before; three had the orbital optic nerve and sheath excised via a lateral orbitotomy 7, 8, and 9 years before, and one patient had the sheath stripped from the nerve 12 years before detection of the intracranial disease.

No patient has died from meningioma in the period of follow-up, which has ranged from three months to 15 years (mean 6.8 and median 6.0 years). There are 15 patients alive and well with either unoperated or definite residual orbital disease, and their ages at presentation ranged from 27 to 78, with most in the older age group. The presence of good vision, the patient's age, or poor general health and lack of serious symptoms were the major reasons for adopting a conservative approach in these patients.

The commonest histological type of tumour seen was a meningothelial meningioma. There were two examples each of the transitional (mixed), fibroblastic, and angioblastic types. Two patients were found at surgery to have cystic expansions of the optic nerve sheath. One had an angioblastic meningioma within the wall of the cyst, and the other had a meningioma at the orbital apex, proximal to the cystic expansion. Both these cases have been reviewed in detail elsewhere.²

Three young patients with intracranial spread were particularly interesting. We present their detailed histories.

CASE 1

This boy presented in 1972 at the age of 10 having had poor vision in the right eye from the age of 5. He had a visual acuity of 6/24 and 5 mm of axial proptosis, and the optic disc was atrophic. There was no family history and no cutaneous manifestations of neurofibromatosis. Ultrasonography, venography, and angiography suggested an intraconal mass. Through an anterior orbitotomy the optic nerve was exposed and seen to be diffusely enlarged in its anterior half, with an intact dura. No biopsy was taken, and a diagnosis of optic nerve glioma was made. A conservative approach was adopted and he was lost to follow-up but returned at the age of 18 with vision reduced to light perception. There were now prominent shunt vessels on the disc. A CT scan showed a heavily calcified optic nerve tumour. In addition bilateral acoustic neuromas, without clinical deafness, were found. The diagnosis was changed to optic nerve meningioma as a manifestation of the central form of neurofibromatosis. There were no cutaneous stigmata. An orbital exenteration was required to clear the orbit owing to its extensive involvement. At craniotomy a small amount of meningioma was found within the middle cranial fossa and removed in continuity with the intracanalicular optic nerve and sheath. He remains well without evidence of recurrent meningioma.

CASE 2

This young woman was first seen at the age of 20 having first noticed poor vision in the right eye at 12 years. This was attributed to amblyopia, but within four years the eye was blind. When seen by us there was 3 mm of proptosis and an atrophic optic disc. There was no evidence of neurofibromatosis. CT scans showed a fusiform enlargement of the optic nerve without intracranial involvement. The optic nerve was exposed via a transconjunctival approach and found to be diffusely enlarged and bluish in colour. A small biopsy was obtained. Histopathology was inconclusive without sufficient evidence for a

diagnosis of either meningioma or glioma. However, optic nerve glioma was thought to be the more likely diagnosis, and the patient was observed. By the age of 28 a repeat CT scan demonstrated calcification of the tumour with intracranial extension. A craniotomy was performed, and a small extension of meningioma from the proximal end of the optic canal on to the jugum sphenoidale was seen. The optic nerve, its sheath, and meningioma were excised with preservation of the globe. There has been no evidence of recurrence in over two years.

CASE 3

A 20-year-old man complained of 15 months' blurred right vision. For one month he noticed that the right eye went completely blind on sustained right lateral gaze, but vision returned to normal within seconds of looking directly ahead. Central acuity was 6/6, but there was only a small intact central field and defective colour vision. The disc was pale and slightly swollen, and there was 2 mm of axial proptosis. A CT scan showed a thickened optic nerve but no evidence of intracranial spread. Angiography showed only minor displacement of the ophthalmic artery. A craniotomy was performed, and the diagnosis of meningioma confirmed. Despite the negative radiology, tumour was found wrapped around the optic nerve for 2–3 mm within the middle fossa. An en bloc excision from the chiasm to the globe was achieved. There has been no evidence of recurrence over a four-year follow-up.

Discussion

Meningioma has long been recognised as a disease mainly of middle age,^{1,4} and our series is no exception. It has also been noted that primary optic nerve sheath meningiomas appear at an earlier age than secondary orbital meningiomas or other intracranial meningiomas.³ In this series the mean age at presentation for optic nerve meningioma was 43.2 compared with 51.1 in 61 patients seen at the orbital clinic with sphenoid ridge meningiomas. Some or all of this age difference is presumably due to relatively smaller tumours in the orbit producing symptoms earlier than a similarly sized intracranial meningioma, especially in a region such as the sphenoid ridge.

This series also shows the usual female preponderance (66%). The presence of significantly larger numbers of males in the younger age groups has not been recorded before, though the trend was noted in our previous paper.⁴ A recent paper reported a 76% incidence of progesterone receptors in a large series of meningiomas.⁵ This may partly explain the age and sex incidence of this tumour and the accelerated growth observed in pregnancy.

The association of neurofibromatosis with optic nerve meningioma is far less significant than for optic nerve glioma. In this series no patient had the peripheral form of the disease, and only one had the central form. In that patient the diagnosis was made after the discovery of the meningioma. Similarly, Walsh⁶ described three cases in children who presented with optic nerve meningiomas as the first manifestation of central neurofibromatosis, and Karp *et al.*⁷ reported on two comparable patients.

In most patients the clinical and radiological diagnosis of meningioma is readily made. Patients usually develop a central field loss with disc swelling or atrophy, sometimes with opticociliary shunt vessels; any proptosis is usually slight. The radiological features are also typical, with thickening of the optic nerve, which is often irregular in outline and is sometimes associated with calcification within the tumour surrounding the nerve.

In a minority it may be impossible to differentiate optic nerve glioma from meningioma even with axial and coronal MRI. Although carotid angiography demonstrates a tumour blush in some meningiomas, it has limited use in our experience and is not a useful means of differentiating meningiomas from gliomas. Jakobiec *et al.*⁸ using CT were able to differentiate the two tumours in 80% of patients. In recent years, using MRI in addition to CT, we have achieved a rate of differential diagnosis above 90%. The correct recognition of these tumours is important in young patients, in whom gliomas are relatively common, and meningiomas, though rarer, behave in a more aggressive and invasive manner and should be removed as early as possible. Biopsy should prove which lesion is present, but the differentiation of the two can be difficult unless substantial amounts of tissue are obtained. Often the presence of fairly good vision prevents this from being done. A possible solution to this dilemma is discussed in the adjoining paper on optic nerve glioma.

The different behaviour of optic nerve meningiomas in the young compared to the middle aged and elderly in our series is an important observation in relation to their management. Walsh⁶ and others^{7,9} have previously observed that optic nerve meningiomas in the young can behave in an aggressive manner, and our results support this view. Our findings that four of six patients under 20 years of age and nine of 20 patients in the next two decades developed involvement of the middle cranial fossa is particularly disturbing when compared with the behaviour of the tumour in subsequent decades (four of 24 patients over 40 developed intracranial disease). This difference is, we presume, due to a more active level of biological activity of the meningotheial cells, though we have no evidence of a different histopath-

ological picture in the two groups. The difference is not produced by longer observation of the younger patients, for our older patients have been watched for as long (range 1–15 years in both groups, median 8 years in the older group and 4.5 years in the younger). Involvement of the optic canal and the posterior surface of the sphenoid occurred in 17 of our patients. Karp *et al*⁷ recorded eight of 25 patients presenting under 20 years of age, three at least of whom had intracranial extension. Spread to the middle cranial fossa must have a grave effect on prognosis, for it is almost impossible to eradicate meningioma once the sphenoid is involved. Surgical removal or radiotherapy may slow the spread of the tumour, but it invariably recurs. Only lengthy periods of observation of these patients will provide evidence of the nature and rate of this spread and the effect of attempts at treating these tumours.

This experience has altered our method of dealing with these tumours. Previously surgery was directed at either decompressing the optic nerve to preserve vision, or excision by stripping the nerve of meningioma, or removing the affected part of the optic nerve together with the surrounding tumour. Incising dura to release pressure on the nerve failed to slow visual deterioration and spread the meningioma into the orbital fat and extraocular muscles, so that exenteration was then the only method of removing the tumour from the orbit. We have not used this technique since 1979.⁴ Stripping meningioma off the nerve has always resulted in total loss of remaining vision, though others have reported preservation of vision in some patients.^{10,11} Frequently we have excised the optic nerve together with the tumour. Unfortunately three of 10 such patients have subsequently suffered sphenoidal involvement, two of them being under 40 at presentation.

Our current management is influenced by the behaviour of the tumour in patients of differing age. Patients whose symptoms begin when they are over 40 years have a lesion which should progress slowly, and there is only a small risk of spread to the middle fossa. Many of these patients do not need treatment, but if the tumour enlarges and produces disfiguring proptosis then either radiotherapy or local excision will improve cosmesis and reduce the chances of recurrence within the orbit. Smith *et al*,¹² and more recently Kennerdell *et al*,¹³ have reported on the efficacy of radiotherapy in slowing the progression of optic nerve meningioma, and we have used their technique on two patients with initially encouraging results.

Patients under 40 years should, we believe, be treated more vigorously. All, eventually, should have the optic nerve excised. If the patient is younger than 30 then the chances of intracranial spread are

considerable. We believe that the tumour should be totally excised at an early stage by a transfrontal craniotomy, so that the whole of the optic nerve from the chiasm to the globe can be removed with its sheath even when vision is relatively good. Between the ages of 30 and 40 years the threat of extension to the sphenoid is somewhat less; these patients can be watched until vision is severely impaired before neurosurgically excising the optic nerve and tumour. In all patients, if there is any doubt on clinical or neuroradiological grounds that the lesion is not a meningioma, then histopathological proof must be obtained, usually by frozen section, before embarking on extensive excision. If the tumour has involved the optic canal and the dorsum sphenoidale, surgical debridement can be pursued and the patient subsequently treated with radiotherapy.

Our study supports the view that the characteristics of primary optic nerve meningioma vary with the age of the patient. In general the younger the patient the more active the meningioma. Therapy should therefore recognise this variation in biological activity, with infrequent intervention in the middle aged and elderly and early excision in the young.

Our thanks are due to all the clinicians who referred these patients, Mr Alan Crockard and Professor Lindsay Symon, neurosurgeons at the National Hospitals, Queen Square and Maida Vale, Dr G A S Lloyd and Dr Ivan Moseley, Radiology Department, the staff of the Medical Illustration Department, and Mrs S J Cole who helped with the typing of the manuscript.

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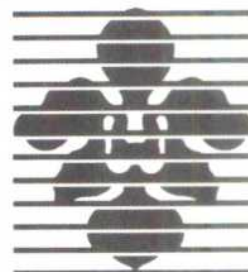
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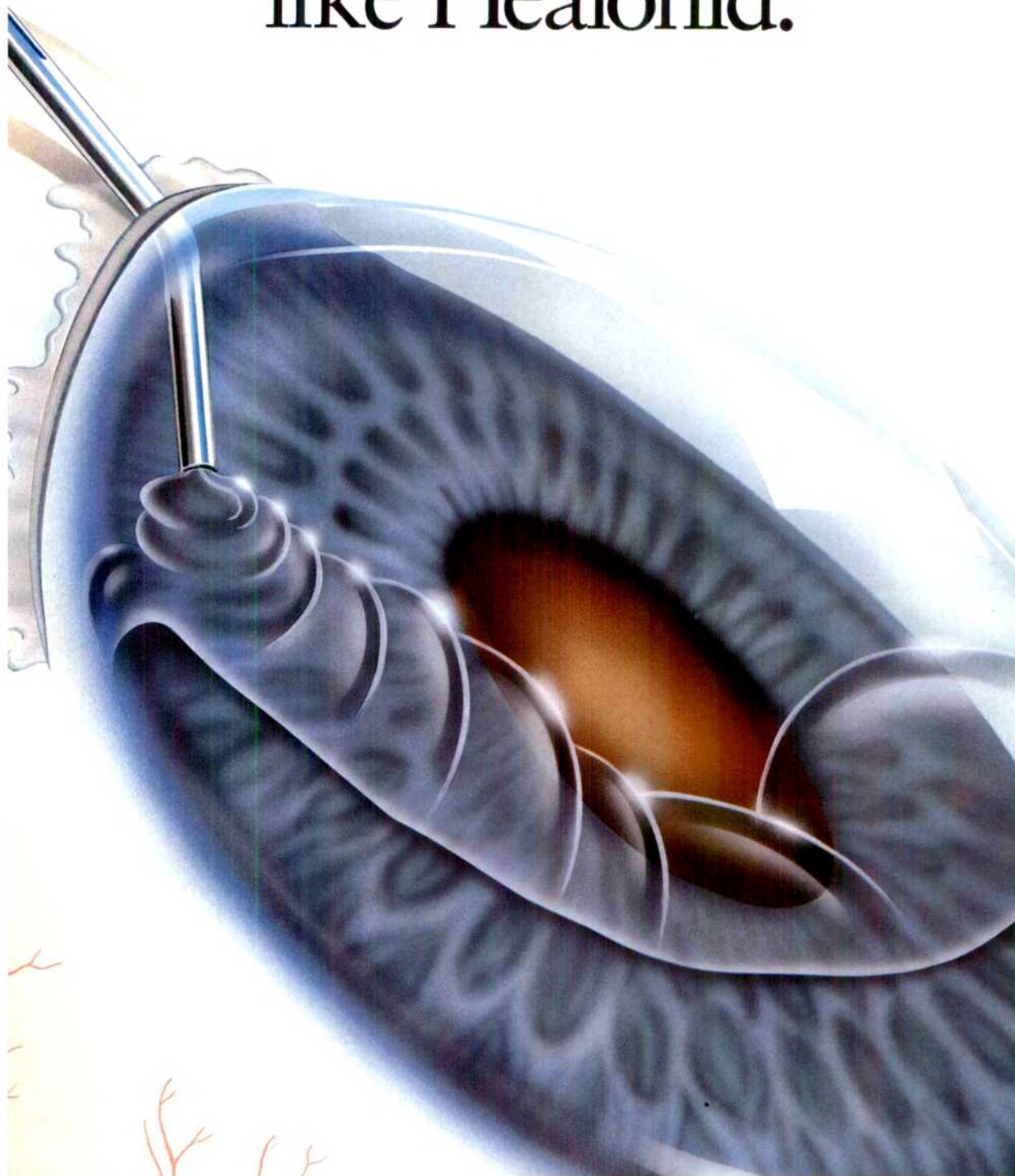
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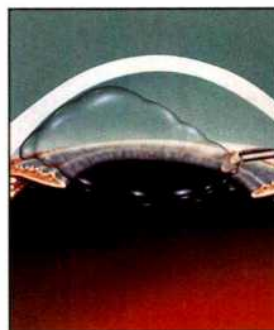
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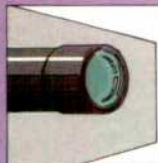
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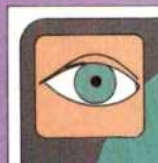
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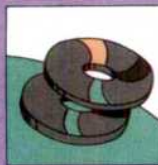
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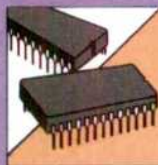
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VISUAL FIELDS

Optic nerve glioma and the management of optic nerve tumours in the young

J E WRIGHT, A A McNAB, AND W I McDONALD

From the Orbital Clinic, Moorfields Eye Hospital, City Road, London EC1V 2PD

SUMMARY Thirty-one patients presenting as orbital optic nerve glioma have been reviewed with maximum follow-up of 14 years. Sixteen of these patients have been reported on previously and further follow-up is provided. Sixteen patients had a stable clinical course with little change over a period of up to 13.5 years. Neurofibromatosis was relatively common in this group (11/16). Fifteen patients had progressive enlargement of the tumour; the incidence of neurofibromatosis in this group was low (4/15). Eleven of these patients were explored neurosurgically and the optic nerve totally excised in 10 of them. The proximal cut end was normal in six patients and the chiasm has apparently remained free of tumour in all of them. We suggest a method of management of primary optic nerve tumours, both meningiomas and gliomas, in young patients.

There is continuing debate about the natural history and management of optic nerve gliomas. Hoyt and Baghdassarian¹ and others²⁻⁴ have claimed that these tumours behave as hamartomas and that they should be managed conservatively. Others have reached different conclusions, stating that these tumours are not benign and self-limiting, and that treatment is required.⁵⁻⁷ In 1980 we reported on 17 patients and demonstrated a division into one group which was stable and another which showed active growth.⁸ One of these patients was subsequently found to have a meningioma, not a glioma as was first reported, and is described as case 1 in the accompanying paper.⁸ Since then we have seen a further 15 patients and they too have fallen into one of these two groups. We have adopted a radical surgical approach in those patients with evidence of active growth and without evidence of chiasmal involvement. In this paper we report our results and follow-up of 31 patients with this uncommon condition.

Patients and methods

Since 1973 we have seen 31 patients with an initial diagnosis of optic nerve glioma. The diagnosis was made on the basis of typical clinical and radiological findings, and in 16 patients in whom diagnostic tissue

was obtained our clinical diagnosis was confirmed histopathologically.

We have excluded the small number of older adults with the highly malignant form of optic glioma (glioblastoma), which usually involves the intracranial visual pathways and follows a quite different course.⁹

A detailed clinical and family history was obtained and a full ocular and neurological examination performed in each patient. Visual fields were charted whenever possible, and most patients had pattern visual evoked potentials (VEP) recorded. Patients were carefully examined for stigmata of von Recklinghausen's neurofibromatosis by the criteria of Crowe and Schull.¹⁰ Plain skull films with optic canal views were routinely performed, and since 1975 all patients have had CT scans at presentation. In recent years most patients have also undergone magnetic resonance imaging (MRI).

The patients were assigned to two groups, (1) those with a 'stable' course and (2) those with 'active growth', on the basis of changes in vision and/or proptosis. A change was indicated by either the history (patient's or relatives' observations) or follow-up examination. For inclusion in the stable group our criteria were: (a) unchanged or improved vision, or vision worsening by less than 2 lines over a minimum period of two years, and (b) proptosis unchanged, decreasing or increasing by 2 mm or less over a minimum of two years. For inclusion in the

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active growth group the criteria were (a) visual loss at the rate of more than 2 lines in a year, or (b) a rate of increase in the proptosis of more than 2 mm in a year. This leaves a potential gap for 'intermediate' patients. None of our patients qualified for this category.

While the patients had a spectrum of change in vision and/or acuity, they fell clearly into one or other group. For example, patients with active growth usually had a dramatic increase of proptosis over periods of less than a year, whereas those in the stable group remained unchanged or even improved over many years.

Follow-up was every six to 12 months in the group with an established stable course but every two to six months in the group with evidence of active growth.

Clinical, radiological, and electrophysiological investigations were aimed at determining the anatomical extent of the tumour and in particular whether the optic chiasm was involved. Those patients with active growth, poor vision, and no evidence of chiasmal disease were referred to a neurosurgeon for a frontal craniotomy. If the chiasm appeared macroscopically normal, the nerve was transected just in front of the chiasm, and after unroofing the optic canal and orbital roof the involved nerve was removed to the globe.

In patients in whom there was active growth but investigations revealed an involved chiasm surgery, when required, was confined to the reduction of the disfiguring proptosis by means of an anterior approach, or a ventriculo-atrial shunt for obstructive hydrocephalus.

Biopsy of the optic nerve has not been performed for many years because the results can be misleading.⁵ Radiotherapy was not used routinely, and only two patients have had this form of treatment. Squint surgery was occasionally performed for cosmetic purposes and enucleation was required in several cases.

Results

CLINICAL FINDINGS

A total of 31 patients has been seen with a clinical diagnosis of optic nerve glioma. The details of their age and sex distribution are shown in Table 1. The presenting symptoms are outlined in Table 2 and the physical findings in Table 3. Fifteen of the 31 patients had neurofibromatosis (48%). All had reduced acuity at presentation, with 15 having 6/60 or worse vision (Table 4). the average degree of proptosis was 3.0 mm, but six had no measurable proptosis whereas one was proptosed 8 mm. All but one patient had a relative afferent pupil defect, and this patient was found to have bilateral optic nerve involvement on CT but had presented with unilateral proptosis and

visual failure. The ocular motility disturbance most commonly seen (14/31) was a limitation of elevation of the globe, which in many cases was quite marked.

RADIOLOGY

An enlarged optic foramen on plain x-ray was found in 25 patients at presentation. Twenty-six patients had CT scans at presentation (Fig. 1); 24 showed a mass involving the optic nerve without apparent involvement of the optic chiasm. Two showed obvious chiasmal enlargement and two incidental enlargement of the contralateral optic nerve. These changes were unsuspected on the basis of clinical examination.

Magnetic resonance imaging (MRI) has been

Table 1 Age and sex data

Total patients	31	
Sex	Male 7	Female 24
Involved nerve	Right 15	Left 16
Age at presentation	Mean	10.2 years
	Median	6.5 years
	Range	2-38 years

Table 2 Presenting symptoms

Proptosis only	12
Proptosis and visual loss	9
Visual loss only	3
Proptosis and squint	3
Squint and visual loss	2
Squint only	1
Pain, visual loss, and obscurations on lateral gaze	1

Table 3 Physical findings

	Present	Absent
Poor vision	31	~
Proptosis	25	6
Relative afferent pupil defect	30	1
Enlarged optic canal	24	7
Neurofibromatosis	15	16

Table 4 Visual acuity

Vision	Number
6/9-6/12	5
6/18-6/24	6
6/36-6/60	9
CF-HM	4
PL	3
NPL	4

CF=counting fingers. HM=hand movements. PL=perception of light. NPL=no PL.

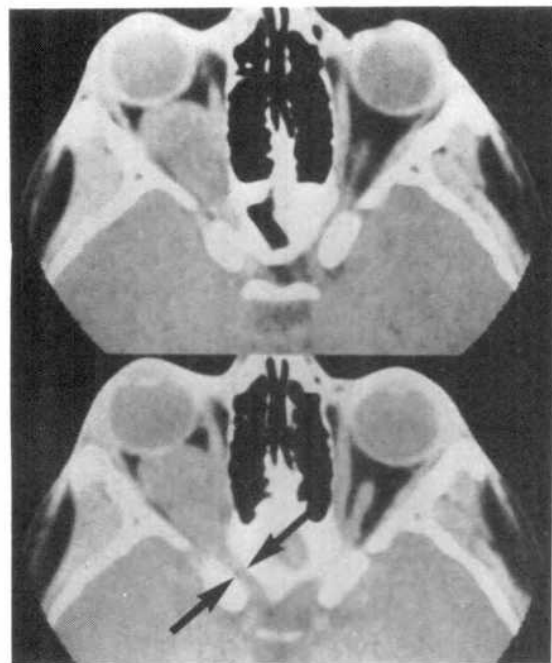


Fig. 1 Axial CT, without contrast, of a patient with an active glioma involving the right optic nerve. Note the typical fusiform outline of the tumour and the enlarged optic canal (arrowed).

particularly useful for demonstrating the extent of tumour (Figs. 2 and 3). In two patients it has detected chiasmal involvement when both CT and VEPs were normal.

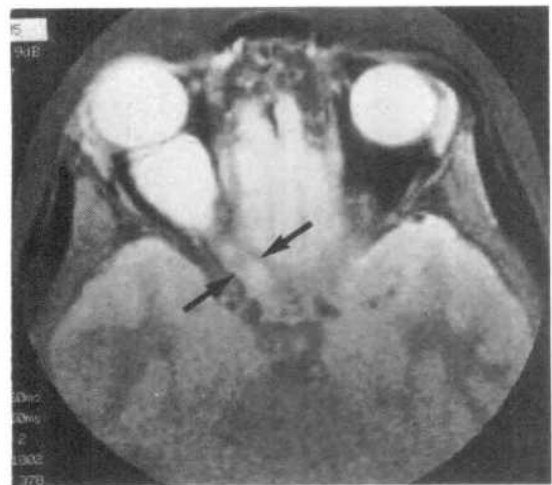


Fig. 2 Axial MRI of the same patient as in Fig. 1. Note the improved definition of the enlarged optic nerve in the optic canal (arrowed).



Fig. 3 Coronal MRI of the same patient in Figs. 1 and 2 showing involvement of the optic chiasm (arrowed).

CLINICAL COURSE

Stable group

Eight of nine patients reported in 1980¹ as having a stable clinical course have not shown evidence of active growth subsequently. One patient has since been found to have a meningioma and has been excluded from this study (patient 1 in the accompanying paper on optic nerve meningioma²). Eight new patients have been added to this group. The stable group had ages at presentation ranging from 2.2 to 38 years (mean 9.9 years, median 8 years), and at the onset of their symptoms from birth to 30 years (mean 5.9, median 3.5 years). Eleven of 16 had neurofibromatosis. In three patients in whom clinical examination suggested the glioma was confined to one optic nerve CT scans showed thickening of the contralateral nerve in two and the chiasm in the other. The optic disc was atrophic in 14/16 patients, with shunt vessels in one. Only two showed optic disc swelling, which was mild. Visual acuity improved spontaneously in three patients, one from 6/24 to 6/6 over seven years, and minor fluctuations in vision were common. Two patients also had a reduction in their proptosis of 2 and 3 mm in the period of follow-up. The greatest increase in proptosis was from 3 to 6 mm over six years. The remainder were unchanged or had increases of 1 or 2 mm over periods of two to 12 years. Follow-up has ranged from two to 13.5 years (mean 7.2, median 7.0 years). The exception was a patient with a one-month follow-up who presented at the age of 38 with a 27-year history of poor but stable vision and neurofibromatosis. Four patients within this group have been lost to follow-up after 2, 2.5, 3, and 8 years. Another patient within

this group with neurofibromatosis and a five-year follow-up has a mother (not included in this series) with a chiasmal glioma that was irradiated and has remained essentially unchanged over at least 10 years.

Active group

By contrast there were 15 patients with evidence of progressive enlargement of the tumour, eight added since 1980.⁶ These patients presented between the ages of 3.0 and 26.4 years (mean 10.7, median 9.0 years), and their symptoms began between birth and 26.0 years (mean 8.3, median 6.9 years). Only four of this group had neurofibromatosis. Nine had disc swelling, four optic atrophy, one had tumour on the disc, and another a total exudative retinal detachment.

Two patients from the 'active growth' group were confirmed as having chiasmal involvement by CT. One presented in 1974 ('patient 3') with a four-months history of squint and two months' proptosis. During follow-up she developed visual evoked potential (VEP) evidence, and later visual field changes, indicative of chiasmal involvement. A CT in 1974 had failed to show chiasmal involvement but a later higher resolution scan detected it. The second patient presented first in 1973, ('patient 7') and during follow-up developed VEP and then perimetric evidence of chiasmal involvement. Only at this stage did a CT scan disclose an enlarged chiasm, and a pneumoencephalogram confirmed a suprasellar mass. A third patient's chiasmal disease was detected only on MRI.

Follow-up in the 'active growth' group has been from 1.5 to 14 years (mean 7.8, median 6.2 years). No patient has been lost to follow-up. One died after a pneumoencephalogram.

SURGERY

Ten patients with active growth without evidence of chiasmal disease were referred for neurosurgical exploration. Nine had a macroscopically normal chiasm and the optic nerve was therefore excised from the chiasm to the globe. The proximal end of the excised nerve was histologically clear of tumour in six patients and involved by tumour in three patients. One patient had an enlarged chiasm and the tumour was merely biopsied. A further patient had an orbital glioma excised through a lateral orbitotomy. Whether the tumour extended into the intracanalicular portion of the nerve is not known.

Three patients required enucleation. One had tumour growth into the vitreous and developed intractable glaucoma. One had massive growth of glioma from a small amount of tumour which was left attached to the globe after the initial craniotomy. The

globe and recurrent glioma were removed together. The third patient had multiple cystic recurrences of the orbital part of the glioma and ultimately required enucleation and marsupialisation of the cyst. Several patients who have had the optic nerve excised have developed signs of ocular ischaemia, but all have retained the globe. The one patient explored via a lateral orbitotomy ('patient 8') had the optic nerve containing a large grade 1 astrocytoma excised. There has been no evidence of recurrence 12 years after surgery.

Two patients with active growth and chiasmal involvement needed debulking of the orbital part of the glioma for disfiguring proptosis and intermittent subluxation of the globe.

In the group with a stable course five have had surgery. In two a biopsy was obtained to confirm the diagnosis. We have since discontinued this practice, as small biopsies tend to give misleading information, and large biopsies compromise vision. Three have undergone cosmetic squint surgery. One patient with neurofibromatosis had a large plexiform neuroma in association with a diffusely enlarged ipsilateral optic nerve. The plexiform neuroma was debulked. The combination of a plexiform neuroma and a presumed optic nerve glioma is in our experience very unusual.

HISTOPATHOLOGY

In 14 of the 15 cases with evidence of active growth pathological tissue was obtained for histological examination. Two specimens were obtained at orbitotomy to debulk tumour in patients with known chiasmal disease. Eleven specimens were excised optic nerves, and one was a biopsy obtained at craniotomy. In 11/14 a typical grade 1 pilocytic astrocytoma was found. Arachnoid hyperplasia was prominent in seven. Three were considered to be grade 2 astrocytomas. These three all had microscopic involvement of the cut proximal end of the nerve but any disease within the chiasm had remained stable. Two patients with a stable clinical course were biopsied via orbitotomy and grade 1 tumours were found. There was no relationship between neurofibromatosis and the pattern or grade of glioma.

FURTHER CLINICAL COURSE

Of the three patients in whom tumour was present in the proximal end of their excised optic nerve, only one has shown evidence of advancement of the residual intracranial tumour, with the development of mild disc swelling, an inferonasal field defect, an abnormal VEP and involvement of the chiasm and the contralateral optic nerve visible with MRI (but not CT). These changes have remained stable over five years, and central vision remains 6/6 seven years after craniotomy. This patient also developed an

orbital recurrence from tumour left attached to the globe and required an enucleation. No further orbital recurrence has occurred. In the two other patients there has been no clinical or radiological evidence of tumour growth within the chiasm over periods of six and nine years, but one of these patients developed multiple cystic orbital recurrences and finally required enucleation.

None of the six patients in whom the chiasm was clear after excision of the optic nerve has evidence of recurrent chiasmal disease after being followed up for 2, 3, 5, 9, 10, and 10 years. One developed an orbital recurrence requiring enucleation and then partial exenteration for a further recurrence. The orbit is free of tumour after five years. One patient whose glioma was removed via a lateral orbitotomy has had no chiasmal involvement after 12 years. We do not know if the canalicular part of the optic nerve is free of tumour.

Discussion

The natural history and management of optic nerve gliomas remains controversial. Some authors¹⁻³ believe them to behave like hamartomas which are incapable of extension along the nerve into the chiasm and therefore offer no threat to the vision of the other eye. Worsening vision or involvement of the contralateral field is attributed to an increase in the pressure of a pre-existing lesion on near-by axons rather than evidence of true extension into previously uninvolved tissue. We disagree with this concept. The evidence from our present study supports the views we expressed in 1980.⁵ At that time we concluded that patients with optic nerve glioma fell into two fairly distinct groups, one with an indolent course and little change in the size of the tumour, and the other with progressive tumour enlargement. Having followed up these patients for a longer period and added new patients to the series, our conclusions remain the same. Two papers have recently added support for this view. Alvord and Lofton⁷ reviewed the literature and applied actuarial analysis to 623 cases of optic gliomas of which 155 occurred in the optic nerve. They concluded that gliomas have a very wide but continuous range of growth rates; some grow rapidly probably by simple exponential doubling at a constant rate, but the majority behave as though growth decelerates. Wong *et al*⁶ have published a reanalysis of the University of California, San Francisco, experience. Several of their patients had been the subject of Hoyt's studies,⁸ but they reached a different conclusion, namely, that optic gliomas are not benign, self-limiting lesions and should be treated.

Deciding whether patients had an inactive or active

lesion was usually straightforward. Most patients had an initial period of growth of the lesion with progressive proptosis. A minority of those with an inactive lesion had little or no proptosis at any stage, and poor vision was noted either accidentally or at routine school examination. The majority progressed to a period of quiescence, which we have observed to last as long as 13 years, with one patient reporting an interval of 27 years. Some while under observation experienced a reduction of proptosis and improved visual acuity. Active progressive gliomas continued to enlarge, with worsening vision and increasing proptosis usually accompanied by swelling of the optic disc and CT or MRI evidence of growth of the tumour.

The frequency of disc swelling and restriction of ocular movement in patients with active lesions is probably due to enlargement of the tumour. Nine patients had disc oedema compared with only two in the inactive group, where optic atrophy was much more common (14/16). Similarly, restriction of movement of the eye, usually limitation of elevation, was present in 11 patients with active growth, whereas only three patients with a stable course had any reduction of movement of the globe.

The most striking difference between the two groups was the higher incidence of neurofibromatosis in patients with a stable course (11/16) compared with those with active growth (4/15). The tendency for gliomas of the optic pathways, when associated with neurofibromatosis, to behave in an indolent manner has been noted previously.¹¹⁻¹⁵ The overall incidence of neurofibromatosis in our patients was 48%. This is comparable to that observed in some other reports,^{12,13} but rates in other series have been lower (10-30%).^{4,15,16}

We have shown in this series that, while half of the optic nerve gliomas remained quiescent, the remainder enlarged. The crucial question is whether this enlargement is due to division of tumour astrocytes with spread along the optic nerve or is merely an increase in bulk caused by the accumulation of mucin or an associated desmoplastic reaction in the meninges. While the increase in the bulk of the tumour can be easily demonstrated with CT or even better with MRI,¹⁷⁻¹⁹ it is extremely difficult to define the extent of the astrocytoma. The histopathologist examining appropriately stained sections of tissue obtained from the edge of a glioma will often find it difficult to distinguish between abnormal and normal astrocytes. Abnormal astrocytes can be present in the optic nerve or chiasm without significant enlargement, as evidenced in our patients, where the chiasm looked normal but there was tumour at the site of excision. The most sophisticated imaging techniques currently available are therefore incapable of defining the true edge of a glioma.

Physiological tests can be used to determine the extent of lesions within the optic pathways.²⁰ Visual evoked potentials produced by stimuli in different parts of the visual fields or careful evaluation of the visual fields will demonstrate functional defects produced by tumour. However, quite extensive gliomas often cause only minimal compromise of conduction, since these tests, like the imaging techniques, underestimate the extent of a glioma. This was exemplified by the three patients with an active glioma where tumour was found in the cut end of the optic nerve and assiduous examination of the contralateral visual field and VEP studies failed to demonstrate any abnormality of chiasmal function, though one developed a field defect after 24 months. Lewis *et al*²¹ CT scanned 217 patients with neurofibromatosis and found tumours of the anterior visual pathways in 15%. Two-thirds of these tumours were entirely unsuspected. Similarly Spencer³ reported cases of bilateral thickening of the optic nerves when clinically only one eye was affected. Two of our patients had a similar abnormality.

The difficulties in determining the natural history of these lesions was only partly due to our inability to assess their extent accurately. An even more important factor was our decision about eight years after the start of our study to excise the more rapidly growing and presumably more aggressive tumours.

During the early years of this study all patients were managed as though the gliomas would behave like a hamartoma. All 16 patients in the quiescent group have behaved in this manner, and none has developed evidence of invasion of the chiasm during quite long period of follow-up. Two of the first five patients with a more active course developed a contralateral field defect. One of these patients died during a pneumoencephalogram which was being carried out to determine the size of the chiasm. These events profoundly altered our attitude to the best way of dealing with these tumours. Subsequently additional evidence was provided by one of the patients in whom the optic nerve was excised, with microscopic tumour at the proximal cut end. This patient then developed a progressive field defect and enlargement of the contralateral optic nerve. We believe that these cases show that an optic nerve glioma does have the potential to expand within or extend into the chiasm in a similar manner to the case reported by McDonnell and Miller²²: an 11-year-old boy with an optic nerve glioma initially confined to the orbit and optic canal developed neuroradiological evidence of intracranial extension to involve the hypothalamus and third ventricle.

The results of surgical intervention have been instructive. One patient of the 10 who had a cranio-

tomy had an enlarged chiasm, and the optic nerve was not excised. Three of the remainder had tumour at the proximal cut end of the nerve, making it probable that the chiasm was infiltrated by tumour even though it appeared normal to the surgeon. MRI, which was not used in any of these patients, may be capable of detecting small areas of involvement better than a surgeon using an operating microscope. None of our patients with normal MRI studies have had histological evidence of tumour in the chiasm, and two patients who had an enlarged chiasm with normal fields and CT scans were detected with MRI. It will be interesting to see to what extent MRI will enable us to select only those patients with an uninvolved chiasm.

There has been no evidence of tumour growth in either the chiasm or the contralateral optic nerve in any of the six patients where the glioma was totally excised during a follow-up period ranging from 2–10 years. In the three patients who had tumour up to the edge of excision, only one has shown an increase in the size of the chiasm with the development of an enlarged contralateral optic nerve associated with disc oedema and an abnormal field and VEP. The central vision has remained stable at 6/6 over seven years. The other two patients have shown no evidence of spread of their residual tumour over periods of six and nine years. This is in direct contrast to the activity and enlargement of the orbital portion of the tumour prior to craniotomy. Others have noted that incomplete removal of juvenile optic nerve gliomas does not necessarily lead to later clinical recurrence,^{23–25} and it has been suggested that removal of the main part of the tumour might remove the stimulus to its peripheral growth.²⁶ It could be argued that even patients with evidence of chiasmal involvement might benefit from removal of the optic nerve glioma, but we believe this approach is unjustifiable without more definite evidence. Further detailed follow-up of these patients will hopefully provide more evidence about the natural history and effect of treatment on this group of patients.

In reviewing our patients over the last 15 years we have concluded that, while some gliomas are relatively inactive and may well have undergone the deceleration in growth which Alvord *et al*⁷ have suggested, others show a higher level of biological activity, with enlargement and worsening of the clinical picture. One cannot equate this growth of tumour with spread along the optic pathway, but there is sufficient evidence from our study and that of others to indicate that these tumours do pose a threat by direct extension of the astrocytoma into a previously uninvolved chiasm. This threat should be removed by total excision of the involved optic nerve particularly where vision is poor. We do not believe

Management of Primary Optic Nerve Tumours In the Young

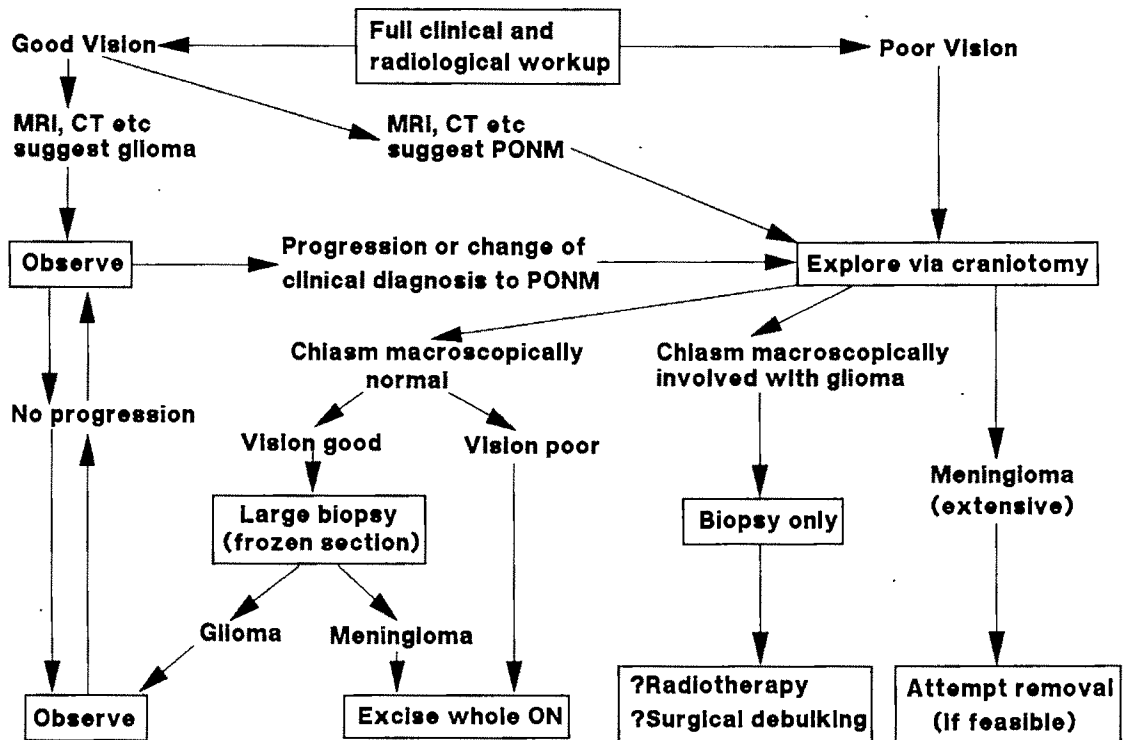


Fig. 4 Flow-chart of recommended management of optic nerve tumours in young patients.

that clinicians who have responsibility for these patients should adopt a totally passive role.

The management of primary optic nerve tumours in young patients without clinical, physiological, or radiological evidence of chiasmal involvement

In another communication⁸ we have drawn attention to the aggressive nature of primary optic nerve meningiomas in young patients. These tumours are capable of invading the middle fossa quite quickly. It is important, therefore, that all primary optic nerve meningiomas which occur under the age of 30 should be diagnosed early and a neurosurgical clearance of the tumour carried out via a transfrontal craniotomy. In the present communication we have shown that a significant proportion of optic nerve gliomas behave in an active manner and can spread from the nerve to the chiasm and affect the vision in the other eye. Their excision appears to remove this threat. In young patients it is therefore logical to excise all primary optic nerve meningiomas and the active group of optic nerve gliomas, preserving the

optic nerve in patients with an indolent or inactive glioma.

In most patients the correct identification of an inactive glioma is not difficult and is based on the typical clinical and radiological appearances.²⁷ However, a few patients have features which make the differentiation of meningioma from glioma very difficult even with MRI. It is always possible that the tumour is a meningioma which can spread aggressively (meningioma cases 1 and 2⁸). This danger can be reduced by excising all optic nerve tumours via a transfrontal approach where vision is poor, a procedure we think justifiable on the grounds that we have seen almost as many patients under the age of 30 with meningioma¹³ as inactive glioma.¹⁶ The pathologist can then decide on the nature of the tumour.

Patients with good vision (6/12 or better)

If MRI and CT scans show an appearance compatible with primary optic nerve meningioma then the patient should be referred for transfrontal neurosurgical exploration. A biopsy should be sent for

frozen section, and if the diagnosis of meningioma is confirmed then the optic nerve should be completely excised together with the tumour. If it is glioma, the optic nerve should be preserved.

The remainder are patients with either a typical glioma or an optic nerve tumour of doubtful nature. These should be observed to see if there is any change in the size of the tumour, the vision, or the characteristics of the MRI and CT scans which would suggest meningioma or active glioma.

Patients with poor vision (6/18 or worse)

These patients should have a transfrontal exploration of the chiasm. If despite the normal investigations the chiasm is involved by glioma, further surgery is not indicated. In all other patients the optic nerve should be excised together with the tumour from just anterior to the chiasm to the posterior surface of the globe. If meningioma has spread into the middle fossa, the neurosurgeon will carry out a microsurgical removal of the tumour, if feasible, and possibly treat the area with postoperative radiotherapy. In occasional patients in whom the history suggests the tumour has been present unchanging for a number of years it may be reasonable to continue to observe the patient.

The accompanying flow chart (Fig. 4) indicates the salient points in our management of primary optic nerve tumours in young patients.

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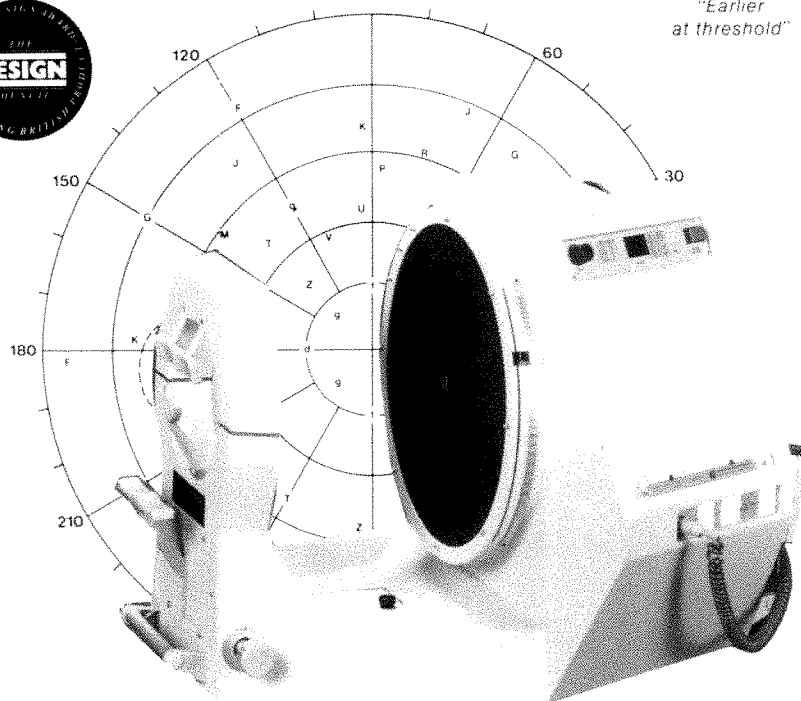
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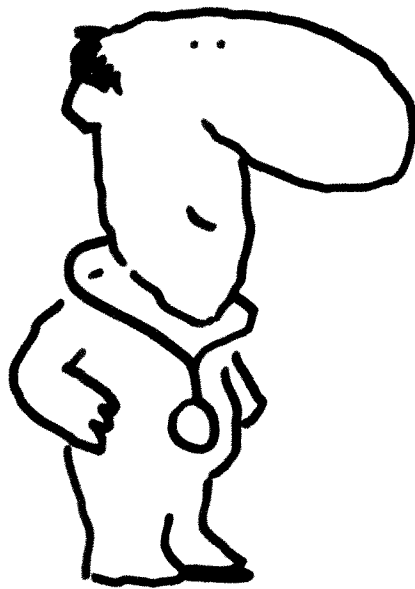


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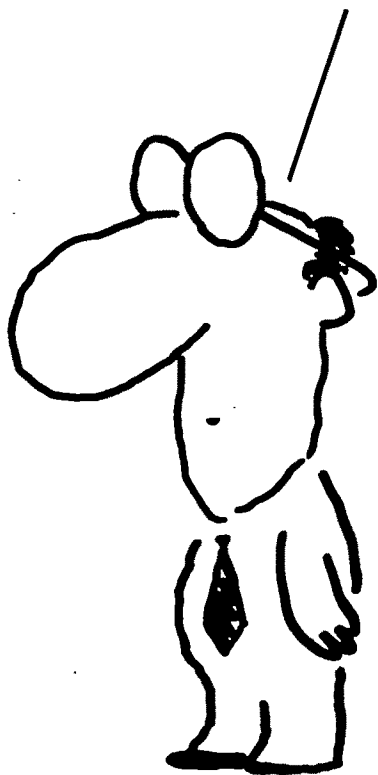
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1. Duzman, E. *et al.*, Am J Ophthalmol 1982; 94 (3): 318-327. 2. Rakofsky S.I. *et al.*, Ophthalmology 1989; 96 (1): 8-11.



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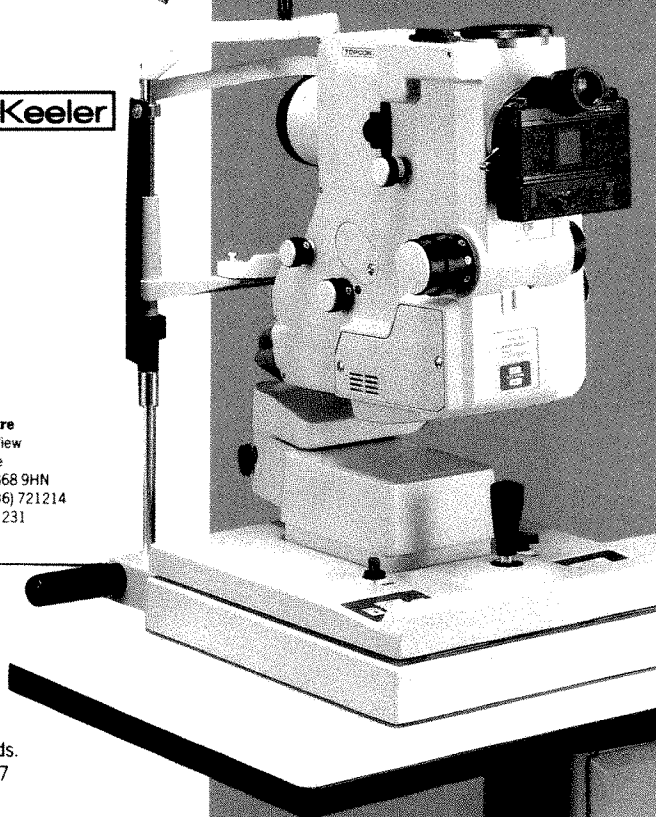
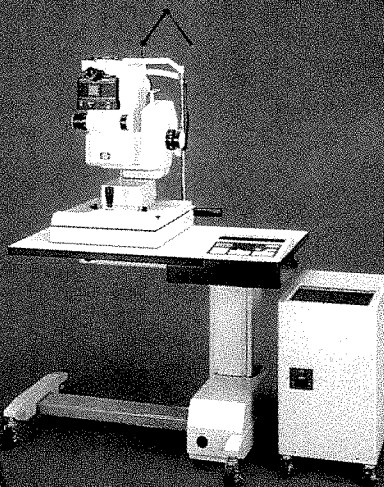
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SUMMARY In 30 patients with previously untreated open-angle glaucoma an intraocular pressure (IOP) curve was taken before and during treatment with PGF_{2α}-isopropylester (PGF_{2α}-IE) eye drops in one eye. Compared with the pretreatment IOP, the PGF_{2α}-IE induced a slowly increasing reduction in IOP. Just before the first dose the IOP was 31.4 (SEM 1.6) mm Hg. When corrected for the fall in pressure observed in the fellow eye the largest reduction, 5.8 (SEM 0.7) mm Hg ($p < 0.001$), was obtained 24 hours later, that is, 12 hours after the second dose. In a subgroup of 10 patients the treatment was continued for one week. In this group the final pretreatment IOP was 25.9 (SEM 1.3) mm Hg. The reduction 24 hours later was 4.5 (SEM 0.6) mm Hg ($p < 0.001$). The effect was maintained and even slightly increased during the week, and on the seventh day of treatment the IOP reduction ranged between 4.8 and 7.6 mm Hg compared with the pretreatment IOP. No serious subjective or objective side effects were observed.

During the last decade the effect of prostaglandin eye drops on intraocular pressure (IOP) has been the subject of many studies. In low doses they are potent ocular hypotensives in rabbits, cats, and monkeys.¹⁻⁶ The drug most thoroughly tested in primates is prostaglandin F_{2α} (PGF_{2α}). Its pressure lowering effect seems to be due to a different mechanism from that of conventional glaucoma drugs. Thus, at least in cats and primates, changes neither in outflow facility^{7,8} nor in aqueous humour production⁴⁻⁶ large enough to explain the effect on IOP have been found. Studies in monkeys indicate that increased uveoscleral outflow may be the major reason for the reduced IOP.⁹⁻¹¹

In studies on the human eye 62.5-250 µg of the trometamol salt of PGF_{2α} reduces IOP 2-4 mm Hg in normotensive eyes, but with unacceptable side effects.¹²⁻¹³ The lipid solubility of the trometamol salt is low, and esterification of PGF_{2α} markedly increases the lipid solubility.¹⁴ Thus an ester such as PGF_{2α}-isopropylester (PGF_{2α}-IE) penetrates the cornea much easier than the parent drug and becomes de-esterified during its passage through the cornea.¹⁵ As

a consequence 0.5-2.0 µg PGF_{2α}-IE is enough to reduce IOP in man.¹⁶ This effect is not due to reduced aqueous humour flow,¹⁶⁻¹⁷ and an effect on outflow facility large enough to explain the effect on IOP was not found in normal eyes.¹⁶ Thus an increased uveoscleral outflow possibly takes place also in the human eye.

Little is known about uveoscleral outflow in humans. In monkeys it is thought to be responsible for 30-45% of the total outflow,¹⁸ but in humans it may be only about 10%.¹⁹ Furthermore, it is not clear to what extent results obtained in young healthy volunteers are valid also for glaucomatous eyes of elderly people. Thus the purpose of the present study is to determine whether the effect of PGF_{2α}-IE on IOP in normal eyes can be verified also in eyes with previously untreated open-angle glaucoma. Some of the results have been briefly reported previously.²⁰

Subjects and methods

DESIGN

The study was designed as an unmasked, open-label study of the effect on IOP of PGF_{2α}-IE. The drug produces some foreign body sensation and conjunc-

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tival hyperaemia even in low doses, and a reliable masking is not possible. Determination of IOP, however, was made in a masked fashion (see below). Thirty patients were selected for treatment during one day (two doses), with the possibility of extending the treatment period to one week in 10 patients if the IOP was adequately controlled during the first day of treatment. Two centres were involved in the study. The study protocol was reviewed and approved by the National Board of Health and Welfare and by the Medical Faculty, University of Umeå.

PATIENT SELECTION

Only patients with previously untreated open angle glaucoma were included in the study. The diagnosis was based on an IOP of more than 21 mm Hg on at least three of five measurements during one day, open angle by gonioscopy, glaucomatous excavation of the optic nerve, and/or glaucomatous visual field defect. Only one eye in each patient was included in the study. In seven patients with suspected bilateral glaucoma the eye with the highest IOP was chosen. The other eye was not treated with any drug during the study. Patients with severe active or chronic systemic disease, a previous history of angle closure or secondary glaucoma, or any concomitant ocular disease were excluded. Eleven men and 19 women between 57 and 79 years of age were included. The diagnosis was glaucoma capsulare in 20 eyes and glaucoma simplex in 10 eyes.

EXAMINATION SCHEDULE

Day 0. A routine ocular examination was performed, including evaluation of the optic disc, the chamber angle, and the visual field (automatic perimetry, Competer). Repeated IOP measurements were made to confirm the diagnosis. The IOP was determined with a Goldmann tonometer, the right eye first. Five consecutive readings were done in each eye with the scale of the tonometer masked to the examiner. The highest and lowest values were discarded, and the mean of the remaining three values was accepted as the true IOP. Before each IOP reading both eyes were examined with a slit-lamp for conjunctival hyperaemia, cells, and flare.

Day 1. No treatment was given, but a pressure curve was taken for both eyes every four hours between 0800 and 2000 and then at 0800 the next morning.

Day 2. After measuring the final pretreatment IOP a 30 µl eye drop containing 0.5 µg PGF_{2α}-IE was applied to one eye of each patient at 0800. A new pressure curve was taken for both eyes. Previous studies with PGF_{2α}-IE have shown a tendency to an initial increase in IOP. For that reason a first measurement was made 30 min after the first dose.

Table 1 Mean IOP and IOP reductions (with SEM) in 30 patients before (day 1) and during (day 2) treatment with PGF_{2α}-IE in one eye. (The final 0800 value on day 1 is the same as the first 0800 value on day 2). 0.5 µg PGF_{2α}-IE was administered after the IOP measurements at 0800 and 2000 on day 2. For definition of IOP reductions and drug related IOP reductions see text

Time	Treated eyes		Untreated eyes	
	IOP day 1	IOP day 2	IOP day 1	IOP day 2
0800	32.3 (1.7)	31.4 (1.6)	21.0 (1.1)	20.4 (1.0)
0830		32.1 (1.7)		19.6 (1.2)
1200	31.1 (1.6)	27.2 (1.6)	19.8 (0.9)	18.6 (0.9)
1600	31.2 (1.7)	26.7 (1.7)	19.6 (1.0)	18.8 (1.2)
2000	29.7 (1.5)	24.3 (1.4)	19.5 (1.0)	18.0 (1.0)
0800	31.4 (1.6)	24.8 (1.3)	20.4 (1.0)	19.7 (1.2)

Time	Reduction in intraocular pressure		
	Treated eyes	Nontreated eyes	Drug related
0800	0.9±0.7	0.6±0.4	
1200	3.8±0.7***	1.2±0.4**	2.7±0.7***
1600	4.5±0.6***	0.8±0.4	3.6±0.6***
2000	5.6±0.8***	1.5±0.4***	4.0±0.5***
0800	6.5±1.0***	0.7±0.6	5.8±0.7***

Asterisks indicate significance levels; *p<0.05, **p<0.01, ***p<0.001.

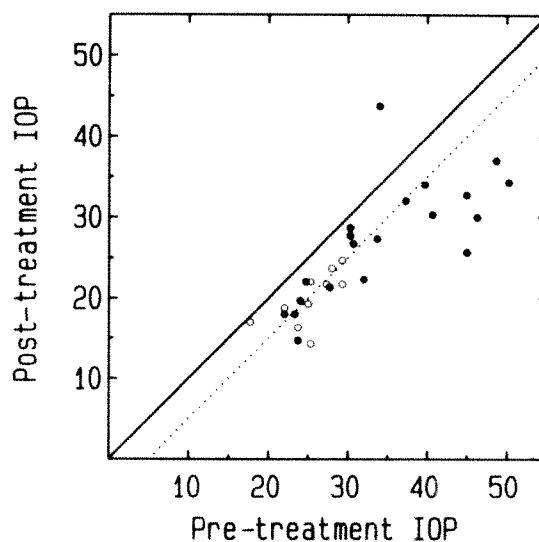


Fig. 1 The effect of two doses of 0.5 µg PGF_{2α}-IE on IOP. Pretreatment values, in mm Hg, are plotted on the abscissa, post-treatment on the ordinate. The value just before application of the first dose was chosen as pretreatment value, that is IOP at 0800 on day 2. Post-treatment IOP is the value 24 hours later, 12 hours after the second dose. The solid line indicates no effect. Points below the dotted line represent eyes where the reduction in IOP exceeds 5 mm Hg. Closed circles: glaucoma capsulare. Open circles: glaucoma simplex.

Apart from that the same time schedule was followed as on day 1. A second dose of $0.5 \mu\text{g}$ $\text{PGF}_{2\alpha}$ -IE was applied after the 2000 IOP determination, and a final IOP was determined 12 hours later, at 0800 on day 3. The participants were questioned about local and systemic symptoms.

Days 3–8. For 10 patients treatment was continued for one week. Inclusion criteria for this second part of the study were no IOP readings above 30 mm Hg after treatment had been initiated and an IOP below 22 mm Hg on at least three of the five IOP measurements during treatment. Fourteen patients fulfilled these criteria; 10 of these were included in the second part of the study. They were treated with two daily doses of $0.5 \mu\text{g}$ in the glaucomatous eye for another six days. This subgroup consisted of one man and nine women, four of them with glaucoma capsulare and six with glaucoma simplex. On days 3 to 7 they were examined daily at 0800 and 2000 with slit-lamp biomicroscopy and IOP determinations. The drug was applied after the IOP determination. On day 8 the procedures for day 2 were followed, with a final IOP determination at 0800 on day 9, that is, 12 hours after the last dose.

EVALUATION OF EFFECT

The pretreatment IOP curve on day 1 was used as control, and the IOP reduction was defined as the change from baseline, that is, the difference (pretreatment IOP minus post-treatment IOP). Prostaglandins are rapidly inactivated in the lungs,²¹ and a contralateral effect induced by systemically absorbed $\text{PGF}_{2\alpha}$ seems unlikely. However, a consensual IOP reduction has been described for several topical

ocular hypotensive drugs.²² To avoid including a possible general effect on IOP we also calculated the 'corrected', drug-related IOP reduction in the treated eye, defined as the difference in change from baseline between treated and untreated eye, that is, (the IOP reduction in the treated eye) minus (the IOP reduction in the untreated eye). The two-tailed Student's t test was used to find statistically significant differences. The results are presented as mean with SEM.

Results

Table 1 presents the IOP on days 1 and 2, the IOP reduction observed in treated and untreated eyes on day 2, and the corrected drug-related IOP reduction in the treated eye, as defined in the 'Methods' section. Four hours after the first dose a highly significant pressure reduction was observed in the treated eye, which remained significant when corrected for the fall in IOP observed in the untreated eyes. The effect slowly increased, and the largest effect was observed 12 hours after the second dose. Fig. 1 presents the IOP just before treatment (0800 on day 2) and 24 hours later, that is 12 hours after the second dose. All but one eye responded with a reduction in pressure. The reduction was more than 5 mm Hg in 18 eyes.

The IOP for the subgroup of patients treated for one week with $0.5 \mu\text{g}$ $\text{PGF}_{2\alpha}$ -IE twice daily are presented in Fig. 2. Treatment reduced the IOP significantly, and the effect remained stable throughout the period of treatment. Before treatment the mean IOP ranged between 23.6 and 26.1 mm Hg, after treatment between 15.5 and 20.4 mm Hg. Table

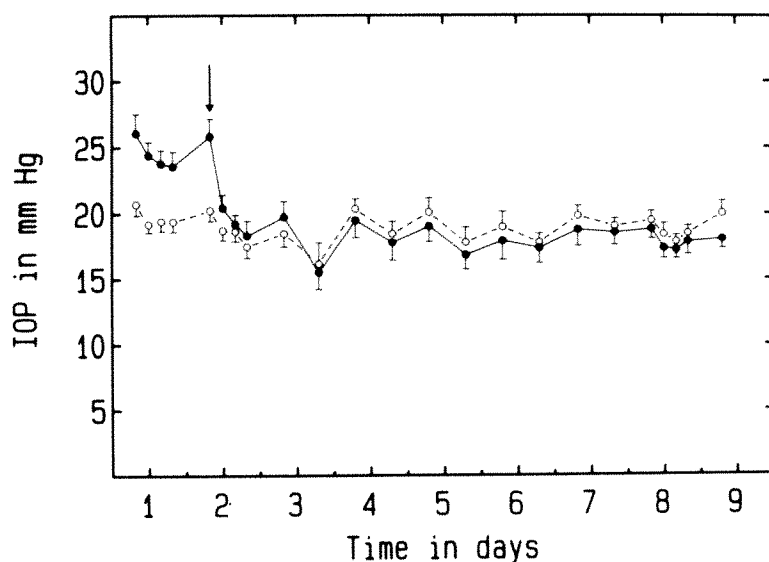


Fig. 2 IOP (mean with SEM) in 10 patients treated with $0.5 \mu\text{g}$ $\text{PGF}_{2\alpha}$ -IE twice daily in one eye for 7 days. The IOP was determined every four hours between 0800 and 2000 on days 1, 2, and 8, and at 0800 and 2000 on days 3–7. Treatment was initiated after the 0800 measurement on day 2 (arrow). The last dose was given at 2000 on day 8, and the final measurement was made 12 hours later. Closed circles: treated eye. Open circles: untreated eye.

2 presents the reductions in IOP observed on days 2 and 8 in these patients. Also in this subgroup there is a significant reduction in IOP in the treated eye from four hours after the first dose, even when corrected for the fall in IOP in the fellow eye. Once again a slow increase in effect is observed during the first day of treatment, and the IOP reduction in the treated-eye is more marked on day 8 than on day 2.

A separate analysis revealed that PGF_{2α}-IE seemed to have similar effects on eyes with glaucoma simplex and glaucoma capsulare. Thus just before administration of the drug the IOP was 34.4 (SEM 2.1) mm Hg in 20 eyes with glaucoma capsulare and 25.3 (SEM 1.1) mm Hg in 10 eyes with glaucoma simplex. The drug related IOP reduction observed 24 hours later was 6.5 (SEM 1.0) mm Hg in glaucoma capsulare and 4.5 (SEM 0.5) mm Hg in glaucoma simplex, that is 19 and 18% of initial, untreated IOP respectively.

A slight to moderate conjunctival hyperaemia was observed in most patients in the treated eyes half an hour after administration of PGF_{2α}-IE. With few exceptions the hyperaemia had disappeared 3–4 hours later. No flare or cells were observed.

About half the patients felt some discomfort in the treated eye for about one hour after application of the drug. This discomfort, mainly in the form of a foreign body sensation, was judged to be slight or moderate, and there was no tendency towards increased or decreased discomfort among the 10 patients that were treated for seven days. No systemic symptoms were reported.

Discussion

In a previous study on the effect of PGF_{2α}-IE on the human eye a dose dependent reduction in IOP was observed, with 0.5 µg at the lower level of the dose response curve.¹⁶ There was a tendency to increased IOP after 30 minutes and then a slow reduction that reached a maximum 8 to 12 hours after application of the drug. A similar pattern was observed in the present study. After a transient small increase the reduction slowly reached its maximum, and the results obtained in the group treated for one week indicate that the maximal effect may not even be reached during the first day of treatment. It must be kept in mind, however, that this subgroup was selected from patients who all responded with a reduction in IOP, and therefore a further increase in effect after the first day of treatment may be a biased observation.

0.1 µg PGF_{2α}-IE had no effect on IOP in normal eyes,¹⁶ and thus it seems unlikely that the decrease in IOP observed in the second, untreated eye is due to a true contralateral drug effect. In fact, a large part of

Table 2 Mean reductions in IOP (with SEM) in 10 patients on the first and seventh day of treatment (days 2 and 8) with 0.5 µg PGF_{2α}-IE twice daily. For definitions of IOP reduction and drug related IOP reduction see text

Time	Treated eyes Day 2	Untreated eyes Day 2	Drug related Day 2
0800	0.2 (1.0)	0.5 (0.4)	
1200	4.0 (0.9)**	0.5 (1.0)	3.5 (1.4)*
1600	4.5 (1.1)**	0.8 (0.7)	3.7 (0.9)**
2000	5.2 (0.7)***	2.0 (0.5)	3.3 (0.4)***
0800	6.1 (1.0)***	1.8 (1.0)	4.3 (0.6)***
Time	Treated eyes Day 8	Untreated eyes Day 8	Drug related Day 8
0800	7.0 (1.2)***	0.8 (0.9)	6.3 (1.0)***
1200	7.1 (1.2)***	0.8 (1.2)	6.3 (1.4)**
1600	6.6 (0.8)***	1.6 (0.6)*	4.9 (0.6)***
2000	5.7 (1.2)***	0.9 (0.7)	4.8 (1.2)**
0800	7.8 (1.1)***	0.2 (0.9)	7.6 (0.7)***

Asterisks indicate significance levels: *p<0.05, **p<0.01, ***p<0.001.

that reduction was observed already before any drug had been applied to the eye. These patients had no previous experience with measurements of IOP, and an obvious possibility is that part of the reduction was due to accommodation to the examination techniques.

A slight conjunctival/episcleral hyperaemia was the only objective side effect observed in the present study. Large doses of prostaglandins may break down the blood-aqueous barrier, and flare and cells have been found in the anterior chamber of experimental animals.¹⁴ No aqueous flare or cells were observed in the present study, which is in accordance with our previous experience with PGF_{2α}-IE in human eyes. In normal eyes topical administration of 0.5–1.0 µg PGF_{2α}-IE for one week has little or no effect on the permeability of the blood-aqueous barrier, even to a small molecule such as sodium fluorescein.¹⁶

The present study was designed to evaluate effects on IOP, and subjective side effects cannot be properly evaluated because local anaesthesia was given for IOP measurements before every drug administration. Among patients treated for one week about half experienced no subjective side effects, while the slight to moderate foreign body sensation reported by half of them seemed to be of the same order as in the previous study on healthy volunteers.¹⁶

In conclusion, topical PGF_{2α}-IE reduces IOP in glaucomatous eyes in elderly patients. The maximal IOP reduction was about 20% of untreated IOP. The pattern of the IOP response and side effects were similar to those described previously for normal eyes in young healthy volunteers.

PGF_{2α}-isopropylester eye drops were generously supplied by Pharmacia Ophthalmics AB, Uppsala, Sweden. The authors have no commercial or proprietary interest in PGF_{2α}-IE eye drops.

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Transient corneal changes associated with the use of gold foil electrodes

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SUMMARY The corneas of 50 normal subjects were examined before and after electroretinography performed with gold foil electrodes. Examination included slit-lamp biomicroscopy and staining with sodium fluorescein. All corneas were normal on examination prior to electroretinography. Three types of transient corneal changes were observed – punctate epithelial keratitis, corneal erosions, and stromal thinning. Each cornea was assigned a numerical damage score based on a simple scoring system. Thirty one subjects (62%) had some degree of corneal change, and in three cases (6%) follow-up was required. Multiple regression analysis was performed to discover any risk factors. Both age of the subject and the use of local anaesthetic were strongly associated with corneal changes.

The use of electroretinography as a clinically useful investigation was facilitated by the introduction of corneal contact lens electrodes.^{1,2} These allowed reliable and reproducible recordings with a stable baseline. Several improvements and refinements to their basic design were made over the next three decades.³ However, such electrodes caused discomfort to the subject and trauma to the corneal epithelium.⁴ This restricted their use in children and in patients with pre-existing corneal disease. A further disadvantage was interference with the optics of the eye, which became important with the introduction of patterned stimuli. The use of foil electrodes^{5,6} and other non-contact lens electrodes⁷ solved many of these problems and enabled longer recording sessions.⁸

We have used gold foil electrodes in our department for both routine electroretinography and research purposes. It has come to our attention that a small proportion of patients suffer transient symptoms after removal of the electrodes and that these symptoms are associated with corneal changes which are visible on slit-lamp biomicroscopy. The symptoms include blurred vision, ocular discomfort, and watering, which occasionally persist for several

days. We have also observed punctate epithelial keratitis (PEK), areas of corneal erosion, and patches of stromal thinning. This paper describes the corneal changes in a consecutive series of normal subjects undergoing electroretinography with gold foil electrodes.

Patients and methods

The subjects participating in this study were a group of normal volunteers undergoing a new ERG protocol which we are developing.⁸ Fifty consecutive normal subjects were included. There were 21 males and 29 females and the average age was 38.6 years (range 20–57). A full medical and ophthalmological history was taken from each subject. Examination included corrected visual acuity, measurement of intraocular pressure, and slit-lamp biomicroscopy, both before and after staining with fluorescein. The pupils were dilated with one drop of tropicamide in each eye, and the subjects were then dark adapted for 30 minutes. At the end of this period gold foil electrodes were inserted under dim red illumination. We used electrodes manufactured in our own laboratory from 19 µm thick gold-plated plastic and electrically conducting adhesive tape.⁹ These electrodes are 20 mm long and 5 mm wide and are taped

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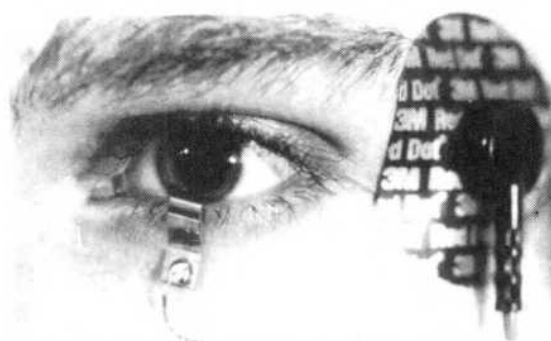


Fig. 1 Gold foil electrode shown in position. The temple reference and forehead earth electrodes are silver/silver chloride types.

to the lower eye lid so that they lie centrally on the cornea (Fig. 1). A local anaesthetic was not used routinely but was offered to all subjects and given if requested or if excessive blinking occurred. If required, one drop of proxymetacaine 0.5% was instilled into each eye.

Multiple ERGs to Ganzfeld stimuli were then recorded over a period of approximately 20 minutes. The intensity of the stimulus was varied by means of neutral density filters from psychophysical threshold to the maximum brightness available from the Grass PS22 photic stimulator. Amplified signals were averaged with computer software with automatic artefact rejection. The number of artefact-free traces required was 32 for low intensity stimuli and 16 for high intensity stimuli. Further details of the electroretinography will not be given here, as they are not directly relevant to the present study. When recordings were completed the electrodes were removed and subjects were examined by slit-lamp biomicroscopy. The presence or absence of limbal injection was noted, and each cornea was graded for the presence of three lesions by means of a simple grading scheme (Table 1). A total score was assigned to each subject, being the sum of the scores for each eye. Thirty minutes after removal of the electrodes the subjects were asked about ocular symptoms, particularly discomfort and watering. They were then allowed to leave and were asked to report back if symptoms persisted.

Results

No abnormalities on slit-lamp biomicroscopy were noted in any of the subjects prior to insertion of the electrodes. Nine subjects (18%) requested the application of local anaesthetic. Thirty minutes after removal of the electrodes eight subjects (16%) complained of some ocular symptoms. The frequen-

Table 1 Scoring system used to quantify corneal changes. Each cornea was assigned a score for each of the lesions shown. The total corneal score for each subject was the sum of all scores for both eyes (maximum 14)

Lesion	Score		
	0	1	2
Limbal injection	Absent	Present	–
Punctate epithelial keratitis	Absent	Less than ¼ of corneal area involved	More than ¼ of corneal area involved
Corneal erosion	Absent	One lesion less than 1 mm in diameter	More than one lesion, or one lesion greater than 1 mm in diameter
Stromal thinning	Absent	One lesion less than ½ stromal thinning	More than one lesion, or one lesion greater than ½ stromal thinning

cies of limbal injection, PEK, corneal erosion, and corneal thinning are shown in Fig. 2. The proportion of subjects who had a corneal sign present in at least one eye was 31 (62%). This may be subdivided into 17 (34%) for corneal injection, 31 (62%) for PEK, 10 (20%) for corneal erosion, and 8 (16%) for

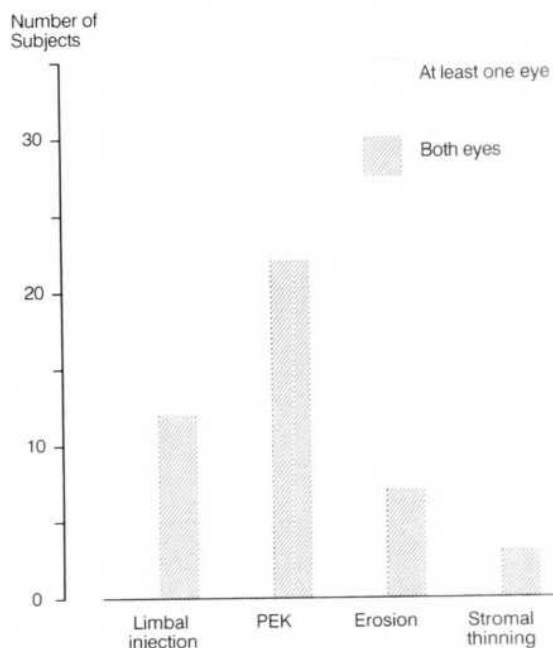


Fig. 2 Frequencies of limbal injection, punctate epithelial keratitis, and stromal thinning. Frequencies are shown for involvement of at least one eye and for involvement of both eyes.

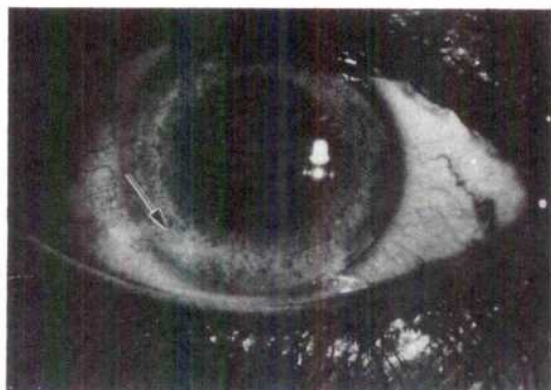


Fig. 3a Slit-lamp photograph of cornea stained with fluorescein. This subject was 21 years old but had not been given local anaesthetic. Note the area of punctate epithelial keratitis lying just nasal to the position where the electrode was placed (arrow).

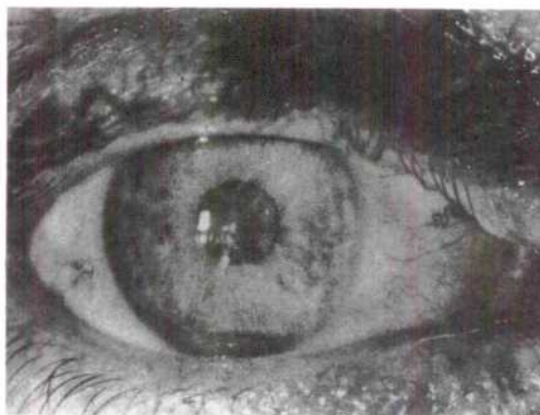


Fig. 3b Slit-lamp photograph of cornea stained with fluorescein. This subject was 27 years old and had been given local anaesthetic. Note widespread areas of corneal erosion.

corneal thinning. Examples of PEK, erosion, and thinning are shown in Figs. 3A, B, C. The affected areas tended to be adjacent to the vertical edge of the electrode. A scatter plot of the total corneal score plotted against the age of the subject is shown in Fig. 4. The relationship between the total corneal score, the use of local anaesthetic, and the subject's age and sex was examined by multiple regression analysis. The total corneal score followed a skewed deviation, so a square root transformation was used to decrease errors which might arise owing to departure from normality. Regression analysis on the

transformed data revealed a significant correlation between total corneal score and two independent variables, age and use of local anaesthetic. Both these correlations were significant at the $p < 0.01$ level. There was no relationship between total corneal score and the subject's sex.

Three subjects (aged 44, 55, and 57, local anaesthetic used in all three) had symptoms which were severe enough for them to return the following day. These subjects had total corneal scores of 10, 11, and 12. Slit-lamp examination revealed persistent PEK.

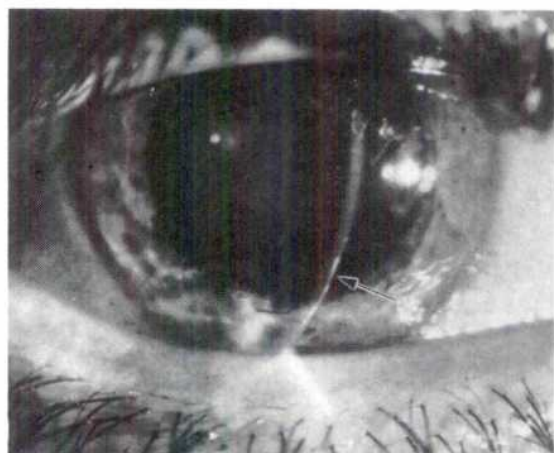


Fig. 3c Slit-lamp photograph of cornea stained with fluorescein. This subject was 51 years old and had been given local anaesthetic. Note the area of localised stromal thinning (arrow). Thirty minutes earlier the thinning was much more marked.

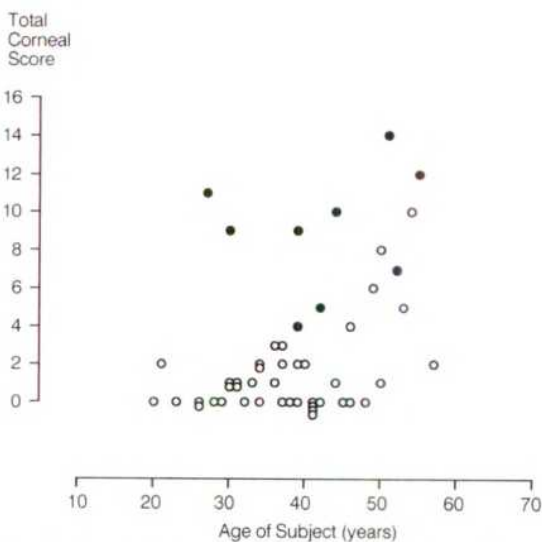


Fig. 4 Total corneal score plotted against age for subjects who were not given anaesthetic (open circles) and subjects who were given anaesthetic (filled circles).

though the other changes which were present the day before had vanished. One other subject (aged 51, local anaesthetic used) with a total corneal score of 14 agreed to remain for photography. At the examination following the ERG corneal thinning was present in both eyes, and in one area the thinning was marked, the corneal thickness being one-third of normal in the affected area. Anterior segment photography was performed 30 minutes later, by which time the thinning had reduced (Fig. 3C). One hour later there was no visible thinning, though erosion and PEK remained. The next day he had no symptoms and all the corneal signs had resolved.

Discussion

The present study indicates that transient corneal changes are common following the use of gold foil electrodes. The proportion of normal subjects with detectable corneal changes in at least one eye was 62%. In eight subjects these were associated with the presence of symptoms, and in three these were severe enough to warrant a return visit the following day. However, all changes were transient, and there were no serious sequelae in any of the subjects or in the several hundred patients who have had electroretinography in our department over the last few years.

There was significant association between the severity of the corneal changes and two factors; the age of the subject and the use of anaesthetic. The relationship with age is probably explained by changes in the composition of the tear film.¹⁰ Local anaesthetic interrupts the afferent pathway and reduces reflex lacrimation. It may also reduce the frequency of blinking, a factor which could well be exacerbated by the absence of a formed visual image in the Ganzfeld stimulator. Local anaesthetic can be toxic to the epithelium,¹¹ but it is unlikely that one drop of proxymetacaine alone could cause the extensive changes observed in this study. Furthermore, of the 31 subjects with some degree of corneal change, 22 had not received local anaesthetic. A weakness of the study is that the use of anaesthetic was decided by the subject and not according to a randomised protocol. It may be that patients requiring anaesthetic have an additional factor leading to corneal changes, such as excessive blinking.

Punctate epithelial keratitis is a non-specific appearance seen in association with a variety of insults to the cornea. Its appearance in this context is most likely related to trauma from the electrode. It is noteworthy that the concentration of PEK was highest near the vertical edges of the electrode. Our electrodes are slightly thicker at 19 μ m than the 12 μ m gold plated Mylar film used by Arden *et al.*⁶ It is also possible that the edges of our electrodes are not as

smooth as commercially available electrodes. However, a visual inspection under a binocular microscope ($\times 50$) revealed no obvious difference between the two. The presence of small corneal erosions is probably also related to trauma. Erosions were present in all eight of the subjects who reported symptoms 30 minutes after removal of the electrodes, and they are the most likely cause of the discomfort. There is a potential risk of corneal infection in the presence of a breach in the epithelial barrier, though we know of no reported cases of infectious keratitis following electroretinography with gold foil electrodes. It may be prudent, however, to administer topical antibiotic to anyone with an erosion. In the light of this the sterility of the electrodes becomes important. Commercially available gold foil electrodes are expensive and tend to be reused, though they are difficult to sterilise. The electrodes used in this study are very cheap and quick to make¹² and can therefore be treated as disposable. This is now our routine practice.

Eight of the subjects in this study had some degree of corneal thinning. This too was commonly seen in the areas adjacent to the vertical edges of the electrodes. This lesion was very similar to dellen¹³ and probably arose through the similar mechanisms. There is evidence to suggest that dellen arise owing to a local deficiency in the tear film¹³ and may be exacerbated by a reduction in blinking.¹⁴ The rapid disappearance of the thinning in one of our subjects over the course of an hour was striking and tends to support the notion that it was related to a temporary disturbance in the tear film.

In summary, we have found a high incidence of transient corneal changes following the use of gold foil electrodes for electroretinography. These changes were associated with the subject's age and the use of local anaesthetic. The following recommendations are made. (1) Local anaesthetic should be used with gold foil electrodes only when absolutely necessary. (2) Patients should undergo slit-lamp biomicroscopy following electroretinography, and if any erosions are present treatment with topical antibiotic should be instituted. (3) Attention should be given to the sterility of the electrodes, and if possible they should be discarded after a single use.

This work was supported by the Sydney Eye Hospital Foundation (Sylvia Kane Bequest for Research into Diabetic Retinopathy) and by Diabetes Australia (Lions Diabetic Retinopathy Research Grant).

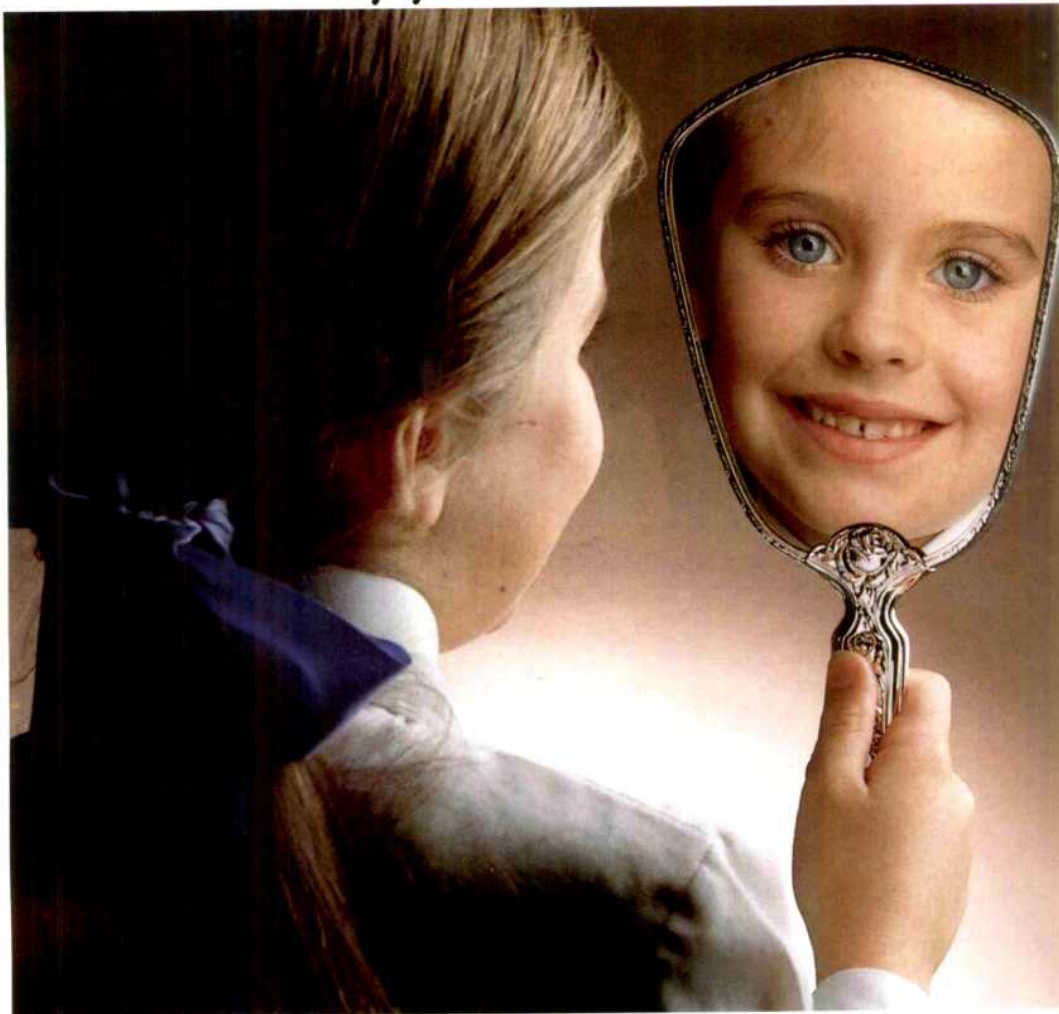
The authors thank the following for their help: Professor G Berry for advice on statistical method; Mr Brett Jeffrey for computer programming and assistance with electroretinography; Mr James Borlaise for photographic processing; and all study participants for their goodwill and co-operation.

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Contra-indications, Warnings, etc.

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Long-term follow-up of acute multifocal posterior placoid pigment epitheliopathy

DAVID F WILLIAMS AND WILLIAM F MIELER

From the Department of Ophthalmology, Medical College of Wisconsin, Milwaukee, Wisconsin, USA

SUMMARY Eleven patients with acute multifocal posterior placoid pigment epitheliopathy were followed up for 47 to 175 months (mean 106 months). Seven of 18 affected eyes (39%) developed progressive mild alterations in the retinal pigment epithelium. Seventeen eyes (94%) had a final visual acuity of 20/30 or better. One eye with progressive retinal pigment atrophy involving the fovea lost visual acuity from 20/25 to 20/60.

Acute multifocal posterior placoid pigment epitheliopathy (AMPPPE) was first described by Gass in 1968.¹ Since then there have been many reports describing its appearance, associated manifestations, course and prognosis.²⁻¹⁸ But there have been few long-term follow-up studies performed.¹⁹⁻²¹ While these have primarily emphasised the long-term visual outcome, one study reported the development of widespread chorioretinal atrophy and associated visual loss in several patients.²¹

The purpose of this report is to provide a long-term follow-up of patients with AMPPPE, with special emphasis on the development of any progressive fundus changes and the effect of such changes on visual outcome.

Patients and methods

Patients with a diagnosis of AMPPPE were identified from the clinic and photography records of the retina service at the Eye Institute of the Medical College of Wisconsin. The patient's history and details of the initial ophthalmic examination were reviewed. Fundus photographs and the fluorescein angiogram were reviewed to confirm the clinical diagnosis of AMPPPE. Diagnostic criteria included the presence of multifocal placoid lesions affecting the retinal pigment epithelium or choroid that blocked chor-

oidal fluorescence in the early phase of the fluorescein angiogram and stained in later phases. All patients thus identified were contacted and asked to return for a follow-up examination.

Follow-up data included the history of the initial episode as well as subsequent ocular history, especially symptoms suggestive of changes in visual acuity and recurrent episodes of ocular inflammation. All patients had best corrected Snellen visual acuity measurements, Amsler grid testing, and pupillary examination. Slit-lamp biomicroscopy, applanation tonometry, and fundus biomicroscopy were also done as well as binocular indirect ophthalmoscopy. The patients then underwent fundus photography and fluorescein angiography.

The details of the follow-up ophthalmic examination were recorded, and detailed comparisons of the initial and follow-up fundus photographs and fluorescein angiograms were made. Special attention was paid to any historical evidence suggesting recurrent disease and to changes in fundus appearance suggesting progression of scarring or retinal pigment epithelial atrophy.

Results

Eleven patients with a clinical history and fundus features consistent with AMPPPE were initially seen between September 1971 and February 1981. Six were male (55%) five female (45%); they ranged in age from 20 to 45 years (mean 31 years, median 29 years) at the time of initial examination. The duration

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Table 1 Patient data

Case/sex/age (yr)	Eye involved	Symptomatic	Visual acuity		Prodrome	Foveal involvement	Concurrent disease	Follow-up (mo)	Progressive pigment atrophy
			Initial	Final					
1/F/44	OD	Yes	20/25	20/20	-	-	-	175	-
	OS	-	20/20	20/20		-	-	-	-
2/M/20	OD	Yes	20/25	20/15	-	Yes	-	151	-
	OS	Yes	20/20	10/15		-	-	-	Yes
3/F/27	OS	Yes	20/50	20/20	-	Yes	-	138	-
4/M/29	OD	Yes	20/60	20/25	Viral	Yes	-	126	Yes
	OS	Yes	20/30	20/25		Yes	-	-	-
5/M/24	OD	Yes	20/25	20/20	-	Yes	-	116	-
	OS	Yes	20/30	20/20		Yes	-	-	-
6/M/29	OD	Yes	20/200	20/30	Viral	Yes	Uveitis	97	-
	OS	Yes	20/200	20/20		Yes	Uveitis	-	-
7/F/26	OD	Yes	20/40	20/20	-	Yes	-	90	Yes
	OS	-	20/20	20/20		-	-	-	Yes
8/M/40	OS	Yes	20/25	20/60	-	Yes	-	88	Yes
9/F/34	OD	Yes	20/30	20/30	-	Yes	-	54	Yes
10/F/34	OS	Yes	CF	20/25	-	Yes	-	47	Yes
11/M/31	OD	Yes	20/20	20/20	Viral	Yes	Uveitis	47	-
	OS	Yes	20/40	20/20		Yes	Uveitis	-	-

of follow-up ranged from 47 to 175 months (mean 106 months). All patients who returned for follow-up examination did so only at our request. None had a recent history of new visual symptoms. Patient data are shown in Table 1.

The presenting symptom in all 11 patients was decreased visual acuity. The duration of ocular symptoms ranged from two days to eight months. Five patients had symptoms bilaterally (45%) and six unilaterally (55%). On examination, however, two patients with unilateral symptoms were found to have lesions bilaterally. Thus of 18 clinically affected eyes 16 (89%) were symptomatic and two were asymptomatic (11%).

Of 11 patients only three had a definite prodromal illness associated with the onset of visual symptoms, consisting of a generalised virus-type syndrome. No patient had taken antimicrobial agents.

The range of initial and final visual acuities are shown in Table 2. Eleven of 18 affected eyes (61%) had an initial visual acuity of 20/15 to 20/30, while

seven eyes (39%) had visual acuities ranging from 20/40 to hand movements (HM). At final follow-up 17 eyes (94%) had visual acuities of 20/15 to 20/30, and one eye (6%) had visual acuity of 20/60. In 17 eyes the final visual acuity was unchanged or improved in comparison with the initial visual acuity. One eye lost visual acuity from 20/25 to 20/60.

None of the 11 patients had a history of previous ocular disease. At the initial ophthalmic examination two patients with bilateral AMPPPE lesions had concurrent bilateral mild uveitis, one with cells only in the aqueous and one with vitreous cells also. All patients had typical creamy white placoid lesions at the level of the retinal pigment epithelium or choriocapillaris demonstrated on fundus photography and fluorescein angiography (Figs. 1A, B, C). In four patients the lesions were acute, with no evidence of early pigmentary changes. Six patients had subacute lesions, with early pigmentary changes in addition to the typical creamy white placoid lesions. One patient had an eight-month history of visual symptoms and appeared to have acute lesions superimposed on chronic pigment epithelial changes. This may have represented a recurrence of AMPPPE.

At final follow-up examination seven eyes (39%) in six patients had developed progressive retinal pigment epithelial alterations. In one patient there were enlarged areas of abnormal retinal pigment epithelium surrounding some of the original lesions. These lesions blocked fluorescence in the fluorescein angiogram (Figs. 2A, B, C, D). One patient had progressive atrophy of pigment epithelium that was subtle but sharply defined and occurred contiguous to the originally involved areas. Four patients developed

Table 2 Range of initial and final visual acuities (18 eyes)

Visual acuity	Initial No. (%)	Final No. (%)
20/15-20/20	4 (22)	12 (67)
20/25-20/30	7 (39)	5 (28)
20/40-20/60	4 (22)	1 (5)
20/70-20/100	0 (0)	0 (0)
20/200-20/400	2 (11)	0 (0)
CF-HM	1 (6)	0 (0)

CF=Counting fingers. HM=hand movements.

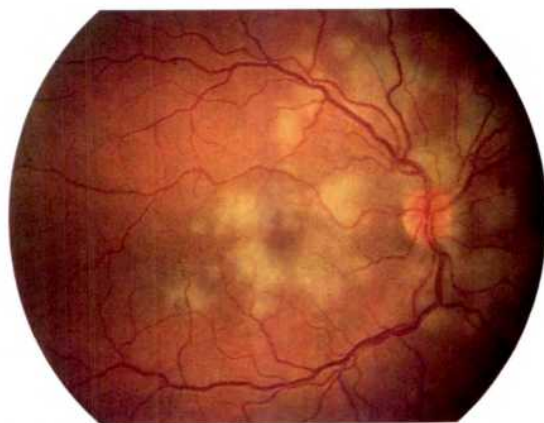


Fig. 1A

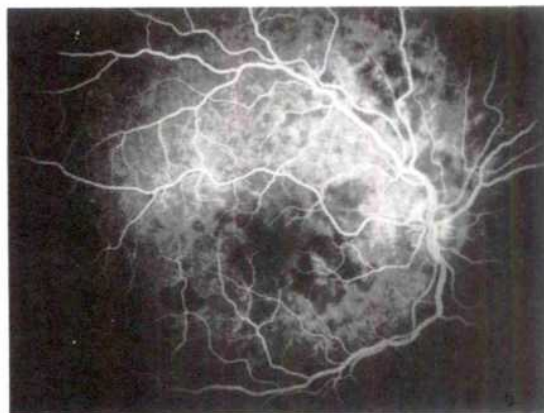


Fig. 1B

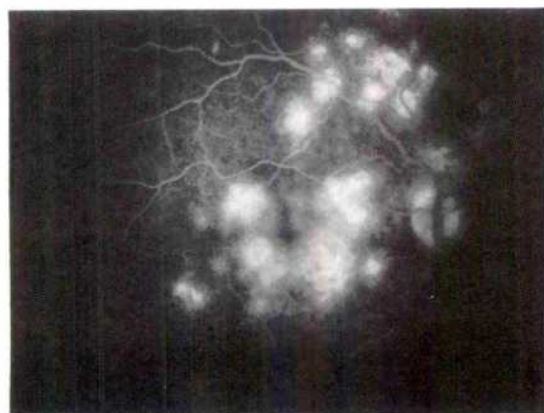


Fig. 1C

Fig. 1 A. Fundus photograph of typical AMPPPE lesions (case 11). Note multifocal placoid areas of creamy-white opacification of the retinal pigment epithelium. B. Mid-phase of fluorescein angiogram. The acute lesions are hypofluorescent. C. Late phase of fluorescein angiogram. The lesions stain with fluorescein.

mild, more diffuse atrophy of the pigment epithelium which involved a larger area and was not always contiguous with the previous atrophic areas (Figs. 3A, B, C, D). In one of these patients the fovea was involved, with a loss of vision from 20/25 to 20/60.

Discussion

Acute multifocal posterior placoid pigment epitheliopathy (AMPPPE) was first described in 1968 by Gass,¹ who reported on three young female patients with bilateral 'rapid loss of central visual acuity secondary to multifocal, yellow-white, placoid lesions at the level of the pigment epithelium and choroid.' The lesions were noted to 'resolve rapidly, leaving permanent alterations in the pigment epithelium and minimal damage to the adjacent choroid and retina.' Vision improved markedly with resolution of the acute lesions and continued to improve for several weeks or months thereafter, such

that the visual prognosis was thought to be relatively good. Since this initial description AMPPPE has also been reported to occur unilaterally in both sexes and in blacks as well as whites.² Many associated ocular findings have been reported, including anterior and posterior uveitis,^{2,8} retinal vasculitis and papillitis,¹¹ serous retinal detachment,¹² retinal oedema and superficial retinal haemorrhages,¹² Marcus-Gunn pupil,¹⁸ and episcleritis.² Systemic findings have included erythema nodosum,^{2,8} cerebrospinal fluid abnormalities,^{18,19} cerebral vasculitis,⁹ and homonymous hemianopia.¹⁷

The anatomical site of primary involvement in AMPPPE is controversial. Some authors have favoured the retinal pigment epithelium,^{1,2,8} while others postulate the choriocapillaris.^{2,6-10} Several reports have documented abnormal choroidal perfusion in AMPPPE,⁶⁻¹⁰ supporting the choroid as the primary site of involvement.

The aetiology of AMPPPE is unknown. The

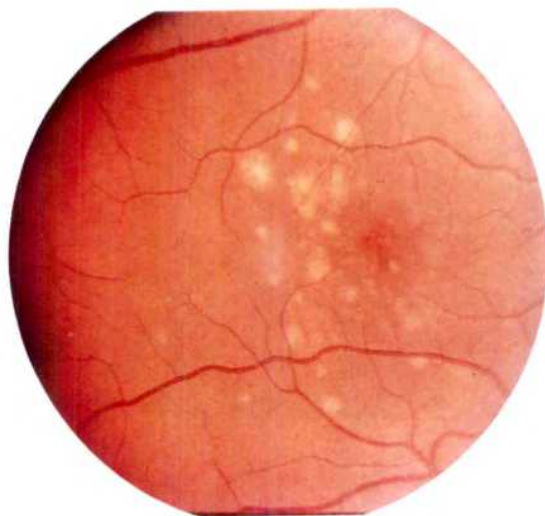


Fig. 2A



Fig. 2B

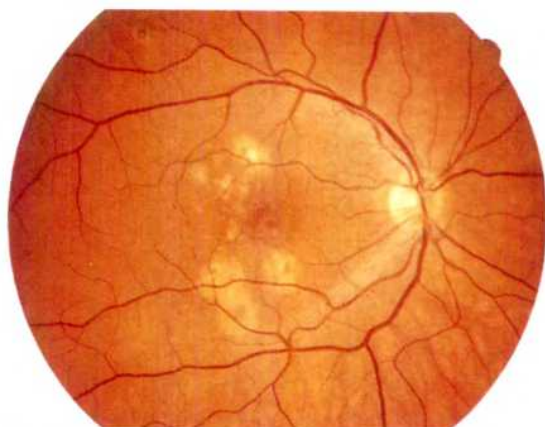


Fig. 2C

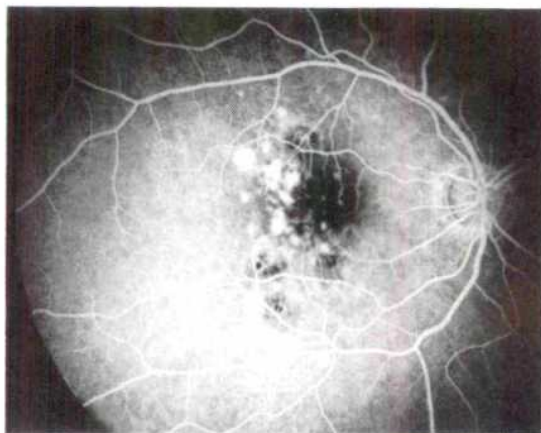


Fig. 2D

Fig. 2 A. Case 7. Fundus photograph of initial AMPPPE lesions. Arrow indicates a lesion which had enlarged at the follow-up examination. B. Initial fluorescein angiogram. C. Fundus appearance 90 months after initial examination. Note enlargement of areas of affected pigment epithelium. D. Fluorescein angiogram demonstrates blocking of fluorescence by enlarged areas of abnormal pigment epithelium.

possibility of an infectious cause is supported by the frequent occurrence of an antecedent viral illness.^{2,3,6,8} One report also documented an adenovirus type 5 infection in association with AMPPPE.¹⁸ Others have suggested that microbial toxins⁷ or antimicrobial agents¹⁴ may elicit a hypersensitivity reaction with associated choroidal vasculitis. This may explain recurrences of AMPPPE.

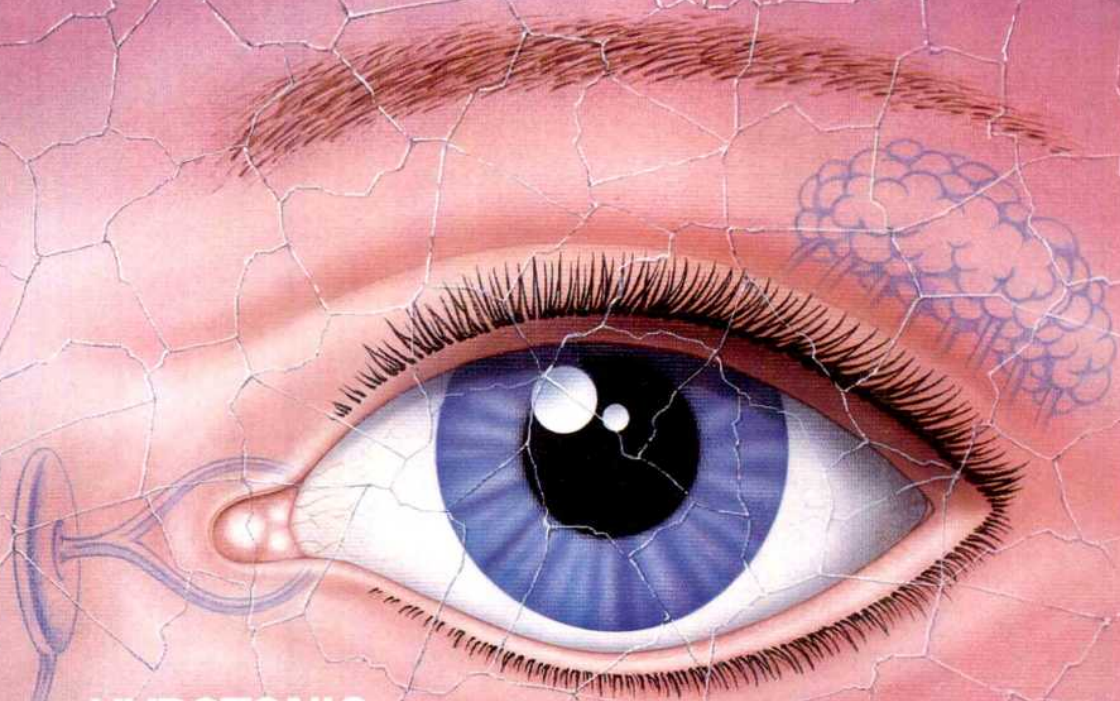
The visual prognosis in AMPPPE is good, with recovery of normal or near normal visual acuity in most patients^{1-3,9,13} within a few months of onset. Long-term follow-up studies have substantiated the

generally favourable visual prognosis,¹⁰ though recurrent disease has been shown to result sometimes in poor visual acuity.^{14,20} Damato and associates²¹ reported on a series of patients with apparent AMPPPE of whom some developed progressive and extensive chorioretinal atrophy with associated visual loss.

In our series of patients the average duration of follow-up was 106 months. Seventeen of 18 affected eyes in patients with AMPPPE had a final visual acuity of 20/30 or better, thus also demonstrating a favourable long-term prognosis. However, seven

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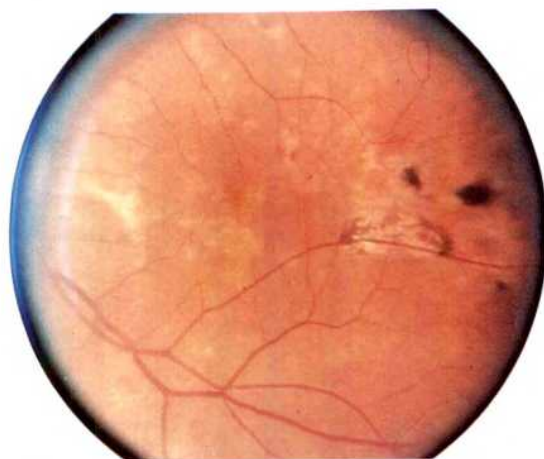


Fig. 3A

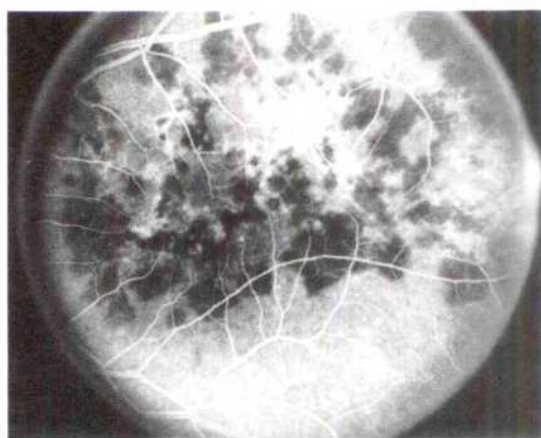


Fig. 3B

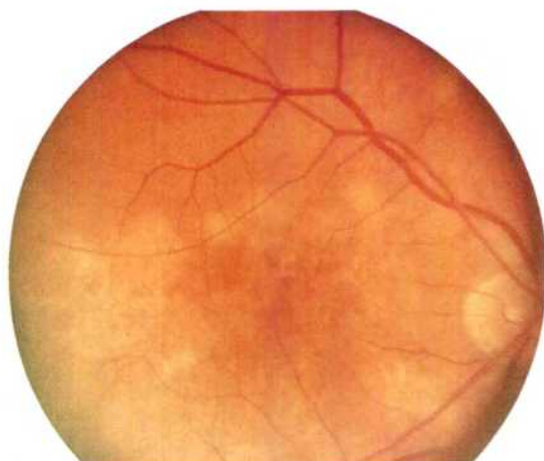


Fig. 3C

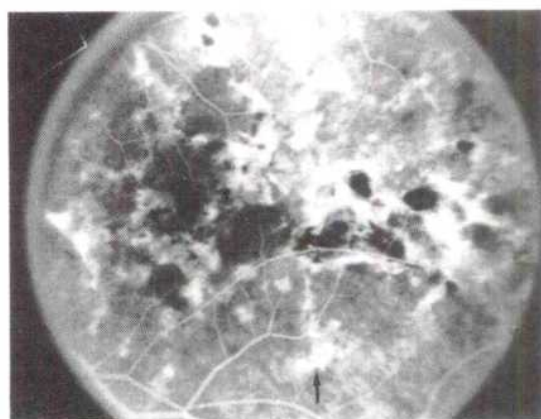


Fig. 3D

Fig. 3 A. Case 10. Fundus photograph of initial AMPPPE lesions. Note extent of lesions inferotemporal to fovea. B. Initial fluorescein angiogram. C. Fundus appearance 47 months after initial examination. Note new area of pigment epithelial atrophy. D. Fluorescein angiogram demonstrates new pigment epithelial atrophy (arrow).

eyes in six patients had progressive pigment epithelial alterations on fluorescein angiography. In contrast to the report by Damato and associates²¹ the progressive changes in our patients were generally subtle and assumed two forms. In two patients (two eyes) pigment epithelial alterations occurred at the margins of the initial area of pigment epithelial involvement. In one of these eyes enlarged areas of abnormal pigment epithelium blocked fluorescence (Fig. 2). In the other some of the original areas of atrophy had enlarged. In four patients (five eyes) mild, more diffuse atrophy of pigment epithelium occurred near to but not always contiguous with the original areas of involvement (Fig. 3). In one of the

last group of patients the area of atrophy involved the fovea, with a decrease in vision from 20/25 to 20/60. Whether the progressive alterations occurred in retinal pigment epithelial cells which were subclinically affected during the initial episode of AMPPPE or as a result of an ongoing active process or recurrence is unknown. However, that no patient had a clinical history suggestive of recurrent or ongoing active disease suggests the former may be more likely.

The differential diagnosis of AMPPPE includes serpiginous choroidopathy, diffuse unilateral subacute neuroretinitis, multifocal evanescent white dot syndrome, vitiliginous choroiditis, and acute retinal

pigment epithelitis.²² AMPPPE is a polymorphic disorder, as shown by the occurrence of a variety of associated ocular and systemic manifestations as well as a wide range in severity and extent of fundus involvement. This polymorphism may make distinction between AMPPPE and related clinical entities difficult. This was illustrated by Wright, Bird, and Hamilton,²³ who described a continuous spectrum of disease from AMPPPE to Harada's disease and emphasised the difficulties in identifying specific diseases within this spectrum. They postulated that these diseases had in common abnormal choroidal perfusion and focal retinal pigment epithelial infarction. Other authors have made similar observations and suggested that diseases within this spectrum are all manifestations of varying degrees of choroidal ischaemia.^{24,25}

This concept may explain the differences in the presence and extent of choroidal and pigment epithelial atrophy in our series of patients in contrast to those of Damato and associates.²¹ Presumably eyes with extensive atrophy suffered more severe choroidal ischaemia than eyes with no or only mild atrophy. Whether eyes that suffer severe visual loss or extensive atrophy and scarring should be considered to have AMPPPE as defined by Gass¹ is not clear. Using the concept of a spectrum of diseases with a common underlying pathogenesis of varying severity may avoid the uncertainties inherent in rigid definitions.

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Fluorescein angiographic findings in three patients with long-term intravitreal liquid silicone

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SUMMARY The long-term retinal effects of intravitreal liquid silicone (ILS) remain controversial. In this study fundus fluorescein angiographic findings in three patients with long-term ILS are presented. Sluggish or absent blood flow was observed in retinal arterioles that lay in close proximity to the ILS, and the arterioles themselves appeared narrowed. It is suggested that ILS may have a long-term effect on the retinal vasculature, owing either to direct vascular damage, secondary to damage to the neuroretina, or to the ILS preventing diffusion of oxygen into the vitreous cavity.

Despite early reports indicating that intravitreal liquid silicone (ILS) is toxic to the retina,¹⁻³ subsequent histological and electrodiagnostic studies have not confirmed this.⁴⁻⁷ In the absence of any clear evidence of retinal toxicity, ILS has maintained its clinical importance, particularly in monocular patients in whom other forms of retinal detachment surgery have failed.

Preliminary work in this institute has identified a possible effect of long-term ILS on the retinal vasculature of a cat, 22 months after ILS instillation.⁸ The silicone occupied one-third of the vitreous cavity, and an area of superior retina was found to be devoid of capillaries after an Indian ink preparation had been prepared (Fig. 1). Prompted by this observation, we performed fundus fluorescein angiography (FFA) on three patients with long-term ILS who had reasonably clear media.

Materials and methods

The case records of 55 patients undergoing retinal detachment surgery involving the use of ILS were reviewed. Three patients satisfied the following criteria: (a) silicone present in the eye for at least one year, (b) anatomically flat retina superiorly, (c) ocular media clear enough to warrant FFA, and (d) patient living close enough to justify recall for angiography. Patients were examined clinically, and consent for FFA was obtained. After colour fundus

photographs had been taken with a Zeiss or Canon fundus camera 10 ml of fluorescein sodium was injected intravenously, and angiographic changes were recorded with a Canon CF 60ZA fundus camera.

Case reports

CASE 1

Male, 78 years. This patient underwent successful bilateral retinal detachment surgery in 1970. In 1975 he underwent left intracapsular cataract surgery and the retina subsequently became redetached. Proliferative vitreoretinopathy (PVR) developed, and two scleral buckling procedures were unsuccessful in reattaching the retina. In December 1980 4 ml of liquid silicone (2000 centistokes) was injected after subretinal fluid had been drained externally and liquid vitreous drained internally. A vitrectomy was not carried out. After eight years visual acuity is hand movements in the left eye, with a clear cornea and normal intraocular tension. Silicone has not entered the anterior chamber because of anterior vitreous membranes. The upper two-thirds of the fundus is in contact with oil and the retina is flat throughout. A high 360° scleral buckle is present. The right eye is pseudophakic and achieves 6/12 visual acuity.

Fig. 2 shows the silicone bubble meniscus inferiorly, and superior retinal vessels appear attenuated behind the bubble. The choroid shows patchy atrophic changes. The FFA (fluorescein is white) shows minimal filling of the superior arteriole at 10 seconds

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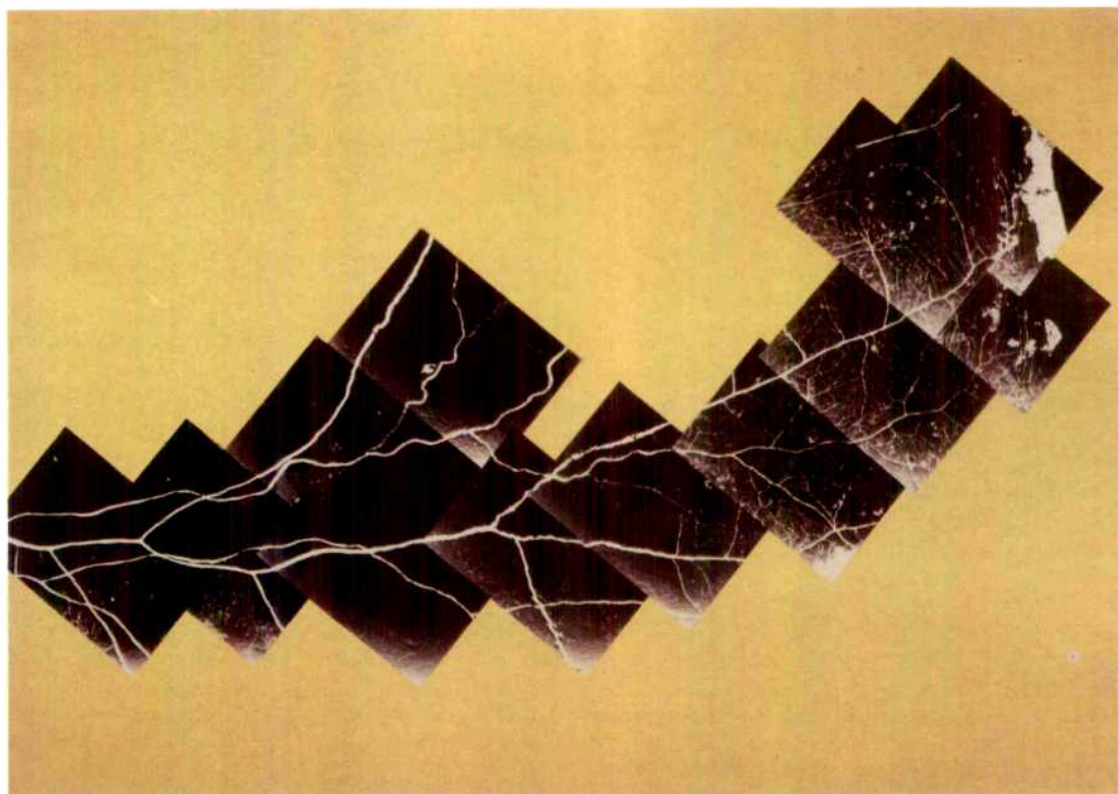


Fig. 1 Composite photograph of India ink preparation showing superior retinal vasculature of cat, 22 months after ILS instillation (optic disc to left). There is extensive small vessel non-perfusion.

(Fig. 3), and at 28 seconds the arteriole remains empty (Fig. 4). The attenuated arteriole superiorly contrasts with the larger vessels below the disc.

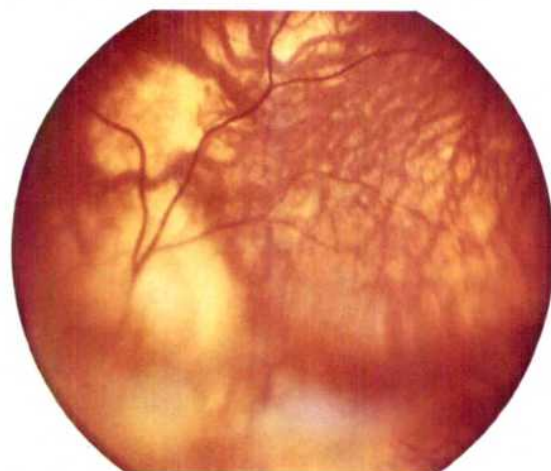


Fig. 2 Superior retina of case 1. Inferior meniscus of silicone oil visible below optic disc.

CASE 2

Female, 66 years. This patient developed a superior rhegmatogenous retinal detachment in the right eye in December 1981. Repair with a radial sponge and encircling band was initially successful, but in January 1982 the retina became redetached inferiorly with



Fig. 3 FFA of case 1 (+10 seconds). There is minimal perfusion of the superior retinal arterioles.



Fig. 4 FFA of case 1 (+28 seconds). Superior retinal vessel attenuation contrasts with vessels below the disc.

development of a fresh tear. After revision of the scleral buckle the retina was successfully reattached, but one month later detachment recurred with development of PVR. In February 1982, 3 ml of liquid silicone (12 500 centistokes) was injected into the vitreous cavity after external drainage of subretinal fluid and internal drainage of liquid vitreous. After six years her visual acuity is hand movements in the right eye, 6/6 left. The right cornea is clear, intraocular pressure is normal, and moderate posterior subcapsular lens opacity is present. A fibrous membrane separates the oil from the lens. The upper half of the retina is attached, the inferior half is detached and rigid. A high 360° scleral buckle is present, and oil fills about one-third of the vitreous cavity.

Fig. 5 shows a deep peripheral buckle, and widespread fibrous encapsulation of the silicone bubble.

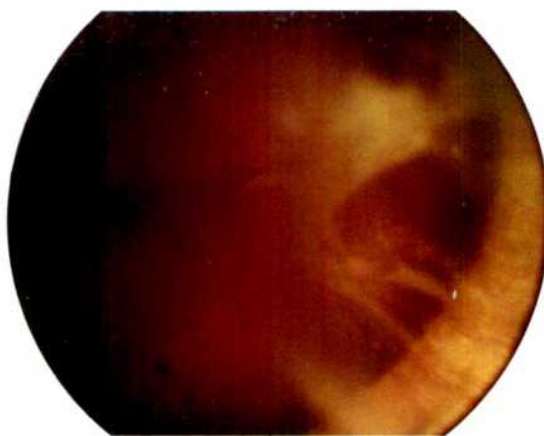


Fig. 5 Superior retina of case 2. The silicone oil is encapsulated with scar tissue. A deep peripheral indent is visible.



Fig. 6 FFA of case 2 (+9 seconds). A narrow retinal vessel behind the silicone oil bubble does carry the dye.

An attenuated retinal vessel behind the bubble is present. FFA shows filling of this vessel at 9 seconds (Fig. 6), and it emptied by 18 seconds.

CASE 3

Male, 33 years. This highly myopic patient developed a large inferotemporal dialysis in his right eye one month after major blunt trauma in March 1982. Conventional detachment surgery was only temporarily successful owing to the development of proliferative vitreoretinopathy, and in July 1982 a vitrectomy with gas tamponade was carried out. This failed to reattach the retina, and 3 ml of silicone oil (2000 centistokes) was injected later that month. After six years his visual acuity is perception of light in the right eye, 6/12 in the left. The patient

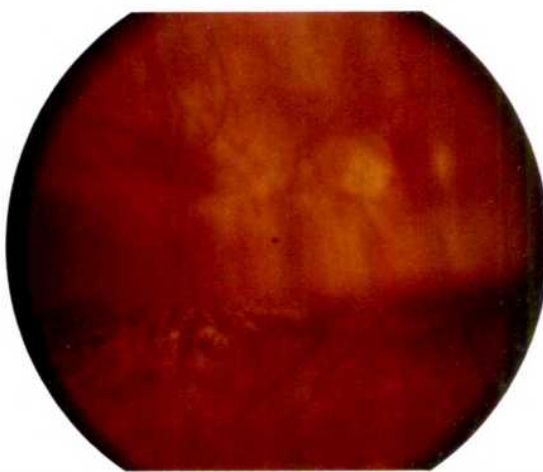


Fig. 7 Superior retina of case 3. The inferior meniscus of the silicone oil bubble obscures the disc. Superior retinal vessels appear markedly narrowed compared with those below.



Fig. 8 FFA of case 3 (+45 seconds). There is no significant perfusion of the retinal vasculature above or below the disc.

is on topical hypotensive medications for chronic glaucoma, and a silicone emulsion is present in the anterior chamber. The iris is rubeotic. The lens is clear, and silicone fills about half the vitreous cavity. The superior two-thirds of the retina is attached, the remaining one-third shallowly detached. The optic disc is widely and deeply cupped.

Fig. 7 clearly shows the meniscus of silicone obscuring the optic disc. Retinal vessels of normal calibre below the disc contrast with the superior retinal vessels, which are hard to discern. FFA shows essentially no filling of the attenuated superior vessels. At 45 seconds there is no fluorescein visible in the retinal circulation above or below the disc (Fig. 8).

Discussion

While long-term complications of ILS such as cataract, glaucoma, and corneal decompensation are well recognised,¹⁰ the long-term effect of ILS on the neuroretina remains a controversial issue.

A clinical study of 407 eyes with long-term ILS stressed that useful vision remained even after 10 years in 25% of initially successful cases.¹¹ Recurrent retinal detachment was the major cause of late loss of vision. Nevertheless clinical opinion is divided on the question of early removal of ILS. McCuen *et al.* recommend removal between three and six months postoperatively,¹⁰ while Casswell and Gregor advocate removal in only a small number of patients.¹²

As a tool in the diagnosis of retinopathy electroretinography (ERG) is limited by the fact that silicone is an electrical insulator.^{6,7} Factors such as quantity of ILS injected, presence or absence of posterior vitreous detachment, and methods of measurement may explain at least part of the variable ERG findings in experimental animals.³⁻⁵

Histological studies on experimental animals have also yielded conflicting results. Lee *et al.*¹ and Mukai *et al.*^{2,3} demonstrated that in monkeys ILS penetrated the retina through breaks in the inner limiting membrane within hours of instillation. Retinal phospholipid was attracted to the main body of ILS, leached out of the retina, and inner retinal layer damage was noted. A toxic retinopathy was postulated on this basis. In contrast Gonvers *et al.*¹³ found that in rabbits retinal damage was limited to the outer plexiform layer, while Ober *et al.*⁴ failed to show any histological changes that could be differentiated from operated control eyes.

To our knowledge there have been no fluorescein studies on long-term human eyes with ILS except for a single case report of a patient six months after ILS instillation.¹⁴ This showed fluorescein leakage inferiorly, adjacent to intraretinal deposits of silicone that had been demonstrated on slit-lamp biomicroscopy. On the basis of this report the authors advocated removal of silicone when intraretinal droplets were clinically apparent.

Fluorescein leakage was not seen in any of our patients, but all showed a marked delay in arteriolar filling under the silicone bubble. A profound loss of retinal capillaries underlying a silicone bubble has been demonstrated in this laboratory in a single cat eye in which the ILS had been present for 22 months.⁸ While this finding remains to be confirmed, it is supported by the fluorescein changes described above. These could be due to a toxic effect of ILS on the retinal microvasculature itself, secondary to damage to the neuroretina, or possibly atrophic in response to high intraretinal partial pressures of oxygen, which would in turn be secondary to the silicone oil resisting oxygen diffusion into the vitreous cavity. ILS is known to act as a barrier to the diffusion of oxygen.¹⁵

An alternative explanation for the observed fluorescein findings is that silicone droplets had invaded the retinal arterioles and mechanically obstructed them. Mukai *et al.* found a single presumed silicone 'spherule' lying within a retinal arteriole during multiple sections of a monkey retina subjected to long-term ILS.² It has been pointed out that some retinas that have been chronically detached respond by progressive narrowing of the retinal vessels when the retina is reattached, with deterioration of visual function.¹⁶ The observation of similar FFA findings above and below the ILS bubble in patient 1, in whom the retina was fully reattached, lends weight to this argument, though the oil was mobile in this patient.

The interpretation of FFA studies on patients such as these is difficult, not only owing to the problems of visualisation, but also to the surgical procedures that

precede the use of ILS. Despite this we believe that useful information can be gained in selected patients, particularly in regard to the question of long-term retinal toxicity involving the retinal vasculature. It is hoped that further studies will be undertaken on suitable patients, preferably in a prospective sequential trial.

We are grateful for the help of our medical photographer Mr Chris Barry for performing the FFA studies and preparing the photographs.

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Long-term outpatient treatment of CMV retinitis with ganciclovir in AIDS patients

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SUMMARY Cytomegaloviral retinitis was diagnosed in nine eyes of seven patients with acquired immune deficiency syndrome (AIDS) on the basis of the characteristic ocular findings and a positive culture for cytomegalovirus (CMV) obtained systemically. Treatment with ganciclovir was begun on a protocol which provided two weeks of inpatient therapy at daily doses of 2.5 to 10 mg/kg followed by outpatient therapy at a reduced dosage three to six days per week. Outpatient maintenance dosage ranged from 15 mg/kg per week to 30 mg/kg per week. In seven eyes of six patients the treatment decreased retinal inflammation and stabilised the margins of the lesions. Six patients have tolerated long term maintenance therapy for 10-30 weeks. Six of seven patients (85%) in this study developed side effects from ganciclovir which required periods of a reduction in dosage or interruption of therapy. The side effects from ganciclovir included neutropenia, thrombocytopenia, drug fever, and neuropathy. Physicians using ganciclovir in AIDS patients must watch for the signs of drug toxicity and adjust treatment accordingly. Ganciclovir appears to be a promising therapy for CMV retinitis, but further work is necessary to determine the best regimen for optimal efficacy with minimal side effects.

In 1982 CMV retinitis was first reported in association with the acquired immunodeficiency syndrome (AIDS). Subsequent case reports have shown it to be the second most common ocular manifestation in patients with AIDS.¹⁻⁸ In these patients the CMV retinitis was observed to be a progressive and unrelenting disease leading to blindness. Trials using vidarabine⁹ acyclovir,^{4,5} or lymphokines⁵ have not produced an observable benefit.

Ganciclovir is a nucleoside analogue which inhibits viral replication by interfering with DNA synthesis within infected cells.¹⁰⁻¹² The drug has been shown to be effective in producing temporary regression and stabilisation of CMV retinitis in patients with AIDS.¹³⁻¹⁷ Recent reports have also documented prolonged stabilisation of CMV retinitis with ganciclovir on an outpatient regimen. Holland *et al.* showed maintenance therapy to be efficacious in 10 patients for at least three weeks and in one patient for up to 33 weeks.¹⁸ Henderly *et al.* treated 23 out-

patients for a similar duration with good results.¹⁹ Because of the importance of this therapy we now report our experience with ganciclovir in patients on maintenance therapy for up to 30 weeks. In our series a higher incidence and a wider variety of side effects with ganciclovir were observed than had been noted previously. In order to maintain patients on therapy lower dosages of ganciclovir were used; these dosages were shown to be more efficacious in stabilising the retinitis or treating recrudescence than has been previously reported.

Subjects and methods

Patients were entered into the drug protocol after informed consent was obtained if the patient was diagnosed as having AIDS, AIDS-related complex (ARC) based on US Clinical Disease Center recognised criteria, or was receiving immunosuppressive therapy for another illness which could not be reduced or discontinued. For the purposes of this report only those patients with AIDS are included.

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The CMV retinitis was confirmed ophthalmoscopically by a retina specialist on the basis of the characteristic clinical appearance. The presence of cotton-wool patches alone was not considered sufficient evidence for entrance into the study. All patients had a buffy coat, urine, throat, or tissue specimen that was culture positive for CMV.

All patients were given inpatient treatment for 14 days before being started on outpatient maintenance therapy. Inpatients were treated with an initial intravenous dose of ganciclovir at 10 mg/kg daily divided into two doses, or 7 mg/kg daily if the patient's peripheral white blood count (WBC) was less than $4 \times 10^9/l$ —a factor for poor tolerance of the full dose due to often observed severe neutropenia (unpublished data). This dose was adjusted for those with renal failure according to the creatinine clearance. If the therapy was discontinued owing to adverse side effects, the inpatient treatment period was extended and based on the length of time the drug was withheld.

Following hospital discharge outpatient maintenance therapy was administered on a schedule of three to six out of seven days by a visiting nurse at the patient's home. The initial outpatient maintenance dose was 5 mg/kg or less, and was administered once daily, based on the response to inpatient dosage and on the occurrence of side effects. Doses were adjusted for alterations in WBC or platelet count. Treatment was withheld if the patient developed a neutrophil count below $1 \times 10^9/l$, if the neutrophil count fell to less than 30% of the admission value, or if the platelet count fell below $80 \times 10^9/l$. Ganciclovir was started again when the neutrophil count rose to $1.6 \times 10^9/l$ or to 50% of the admission value, or when the platelet count reached $100 \times 10^9/l$. If the retinitis progressed on maintenance therapy, the frequency of administration of dosage was increased.

Before they entered the study all patients had a complete history taken and physical examination done, including an eye examination performed by a retina specialist. The patients also had fundus examinations performed on a daily basis as inpatients and on a weekly basis as outpatients. Blood and urine samples were taken before entering the study and on inpatient days 1, 3, 5, 7, 10, and 14 to monitor for haematological, renal, or hepatic side effects. The same studies were also performed on a weekly basis as outpatients. Urine and buffy coat cultures for CMV were obtained at baseline, and on days 1, 3, 5, 6, 10, and 14 of inpatient therapy, as well as bimonthly during outpatient treatment.

Results

This study includes seven sequential AIDS patients

who were treated for CMV retinitis involving nine eyes. Six of the seven patients had stabilisation or improvement of the retinitis during the two-week inpatient induction course (Table 1). One patient could not complete the inpatient regimen as a result of drug intolerance and eventually developed bilateral panretinal necrosis.

In six of seven patients the inpatient induction dosage was 10 mg/kg per day in two daily doses. One patient was on 7.5 mg/kg in divided doses because of pre-existing neutropenia. This patient was able to complete the induction regimen at this reduced dosage. Of the six patients started on a 10 mg/kg/day regimen only two could tolerate the dosage and complete the induction therapy. Four patients developed neutropenia or thrombocytopenia secondary to ganciclovir, which necessitated completing the induction therapy at a reduced dosage or withdrawing therapy.

Six patients therefore entered the outpatient maintenance therapy protocol after discharge from the hospital. (For simplicity the outpatient maintenance dosage is listed as cumulative weekly dosage in mg/kg because the frequency of administration and dosage per administration varied.) Three patients were begun on outpatient dosages of 15 mg/kg/week, given three days per week (5 mg/kg/day). One patient was begun on 25 mg/kg/week given over five days. Two patients were begun initially at a lower daily maintenance dose of 3.5 mg/kg/day given five days per week (17.5 mg/kg/wk).

The cumulative weekly maintenance dosage required to control the retinitis varied between patients. In patient 3 the retinitis was controlled for 85 days with only 15 mg/kg/per week. A relapse occurred after an interruption of therapy, but the retinitis was again controlled with resumption at 25 mg/kg/week. In patient 6 the retinitis was controlled at a level of 17.5 mg/kg weekly for 80 days until he developed a cilioretinal occlusion necessitating the use of corticosteroids. Patient 7 was controlled on 17.5 mg/kg/week for 40 days, and then progression of a macular lesion necessitated an increase in dosage to 25 mg/kg/week, which was successful in resolving the new inflammation and stabilising the retinitis for 50 days. Owing to side effects the dosage was decreased to 15 mg/kg/week, which stabilised the retinitis until day 123, the endpoint of the study.

Patients 1 and 2 were initially started on 15 mg/kg/week maintenance dosage, which at that level caused side effects and was only partly effective in controlling the retinitis. Eventually the side effects necessitated discontinuation of therapy, and both patients eventually went blind. Patient 5 tolerated the inpatient dosage well and was started on an outpatient maintenance dose of 25 mg/kg/week, the

Table 1 Course of therapy and response to ganciclovir of seven patients with AIDS and CMV retinitis

Initial inpatient treatment	Extent of retinopathy	Acuity at onset	Course/response during maintenance therapy	Final VA	Side effects
(1) 10 mg/kg/d then decreased to 7.5 mg/kg/d due to neutropenia	OD clear OS CMV (M, P, V)	6/6 OU	Regression with 5 mg/kg/d (3); stopped after 12 days due to side effects; developed progression of retinitis at day 30; treatment restarted at day 32 at 5 mg/kg/d (6) with stabilisation until day 45; treatment stopped due to side effects day 56; recurrence of retinitis noticed on day 75; no response to lower treatment dosage	NLP OU	Neutropenia Drug fever
(2) 10 mg/kg/d decreased due to neutropenia to 5 mg/kg/d	OD CMV (ON, M, P) OS CWS	LP OD 6/5 OS	5 mg/kg/d (3); OS progressed, however dosage not increased due to persistent neutropenia; treatment stopped day 72; off treatment progression of lesions OD and OS noted day 90; treatment not restarted due to side effects	NLP OU	Neutropenia
(3) 10 mg/kg/d	OD CWS OS CMV (M, MP, V)	6/6 OD 6/15 OS	5 mg/kg/d (3) stable for 85 days; patient withdrew therapy and developed CMV (ON); treatment restarted 5 mg/kg/d (5) on day 103 with retinitis stable until day 160	6/6 OD LP OS	
(4) 10 mg/kg/d developed neutropenia after 5 days; recurrent attempts at decreasing dosage	OD CMV (MP) OS clear	6/7.5 OU	Patient never completed induction therapy due to interruptions in treatment because of side effects at dosages 2.5-10 mg/kg/d	OD CF OS 6/7.5	Neutropenia Thrombocytopenia
(5) 10 mg/kg/d	OD CMV (MP, V) OS clear	6/6 OU	5 mg/kg/d (5) for 28 days stabilisation; treatment stopped due to neutropenia/thrombocytopenia, restarted day 39; 5 mg/kg/d (5), and stabilised to day 66; developed neutropenia; treatment again withheld with progression of retinitis day 84; treatment restarted day 88 at 5 mg/kg/d (3) for 12 days but stopped due to neutropenia; off treatment progression of retinitis; therapy attempted at lower dosage but was inadequate to stabilise retinitis	NLP OU	Neutropenia Thrombocytopenia
(6) 7.5 mg/kg/d	OD CMV (MP) OS clear	6/5 OU	3.5 mg/kg/d (5) stabilised until day 80; developed occlusion cilioretinal artery OS with retinal haemorrhages; varied dosage 3.5-6.0 mg/kg/d for 20 days due to bothersome neuropathy; retinitis then stabilised until day 310 at 6.0 mg/kg/d without further side effects	6/6 OD 6/60 OS	Neuropathy
(7) 10 mg/kg/d developed neutropenia; decreased to 7.0 mg/kg/d and then to 5 mg/kg/d	OD CMV (MP) OS CMV (MP)	6/120 OD 6/6 OS	3/5 mg/kg/d (5) with stabilisation of peripheral lesions but progression of macular lesion; increased to 5 mg/kg/d (5) with clearing of macular region; developed neutropenia; treatment decreased to 3 mg/kg/d (5) with stabilised retinitis to day 175	6/120 OD 6/6 OD	Neutropenia

CWS=cotton-wool spots. CMV=cytomegalovirus retinitis. O=optic nerve disease. M=macula. P=peripheral. MP=midperipheral. V=vasculitis.

5 mg/kg/d (3): number in parentheses denotes frequency of treatment per week.

highest initial outpatient dosage in the series. The therapy was effective in controlling the retinitis initially, but interruptions due to side effects led to progression of the inflammation. Eventually the patient could not tolerate even a lesser dose of 15 mg/kg/week, and the retinitis progressed to blindness.

Side effects which necessitated interruption of treatment or reduction in dosage (or both) included neutropenia (five patients), thrombocytopenia (three patients), drug fever, and neuropathy (one patient).

The drug fever developed 12 days after starting outpatient therapy; the patient was admitted to hospital, at which time no other cause of the fever could be ascertained. The fever resolved with cessation of the drug.

Progression or recurrence of the retinitis was observed within 18 days of interruption of maintenance therapy. If the therapy could be restarted and continued, the retinitis was usually again stabilised or underwent regression. As discussed above, three

patients could not tolerate an adequate dosage of medication, which led to unrelenting progression of the retinitis and blindness.

Conversion of urine and serum buffy coat CMV cultures to negative occurred in five of the six patients who received the complete induction course.

Discussion

Previous reports have documented the efficacy of ganciclovir for short term treatment of CMV retinitis. In a series of 13 patients reported by the DHPG (ganciclovir) Collaborative Treatment Group nine (69%) patients showed improvement in visual acuity or a decrease in retinal inflammation with inpatient therapy.¹³ In several smaller series or case reports ganciclovir has been shown to produce clinical regression and to stabilise the retinitis for up to 30 days.¹⁴⁻¹⁷

In two recently published reports ganciclovir (Syntex) or BW B7596) have been shown to be efficacious for long term therapy on an outpatient basis. Holland *et al.* treated 10 patients with continuous, uninterrupted therapy for at least three weeks.¹⁸ Henderly *et al.*¹⁹ treated 23 patients with interrupted therapy for two weeks to 15 months after the initial diagnosis of retinitis. In our study six patients were maintained on continuous therapy for 10 to 30 weeks. Therapy was interrupted only after development of significant side effects and was restarted as soon as the patient was capable of resuming therapy.

In combining the results of these three series we note that initial induction therapy produced clinical regression of the CMV retinitis in 48 of 50 patients, and outpatient therapy on a lower maintenance dose provided prolonged stabilisation of the retinitis in all patients. Without treatment CMV retinitis is rapidly progressive and destructive. Although ganciclovir inhibits viral replication, cessation of therapy will allow live virus to proliferate. In all patients in this series discontinuation of therapy led to recurrence of the retinal disease. While the goal of therapy is to deliver sufficient drug to control the retinitis, because of the significant rate of induction or exacerbation of severe side effects the physician must carefully monitor for both and adjust the dosages accordingly.

Maintenance dosages varied widely in these three studies both between patients and in any one patient over time. Henderly *et al.* followed up their patients on a standard dose of 25 mg/kg/week with prolonged stabilisation of the retinitis in 70% of patients for up to one year.¹⁹ Holland *et al.* did not specify cumulative weekly doses, but varied their dosage of maintenance therapy widely with good results in 60% of patients for up to 33 weeks.¹⁸ We were able to

maintain three patients on ganciclovir for over 10 weeks with no reactivation of their retinitis at 15 to 17.5 mg/kg/week cumulative dosage.

Throughout maintenance therapy the dose of ganciclovir varied according to the patient's response to therapy and the side effects generated by the medication. It was not unusual to have reactivation of the CMV retinitis on a dosage of the medication which had previously controlled the retinitis. Four of 10 patients followed up by Holland *et al.*¹⁸ on continuous, uninterrupted maintenance therapy had reactivation of the retinitis, and in only one case was this attributed to an inadequate level of drug at 12.5 mg/kg/week of ganciclovir. In the other cases maintenance dosages were higher, though cumulative weekly dosages were not specified. In these patients progression of the retinitis began from six to 17 weeks after the initiation of therapy.

In a study by Henderly *et al.*, while the retinitis was stabilised at levels of 25 mg/kg/wk, 34% of patients developed reactivation of the retinitis at this dosage on an average of 4.6 months after the start of therapy.¹⁹ The retinitis was stabilised with an increase in dosage to 7.5 mg/kg/day for 10 days followed by an increased maintenance therapy of 35 mg/kg/week.

Three of six patients in our study suffered reactivation of the retinitis while on therapy with doses ranging from 15 to 17.5 mg/kg/week. The patients who had recurrences while on 15 mg/kg/week had been on maintenance therapy for less than two weeks. In one case increasing the dosage to 30 mg/kg/week stabilised the retinitis. In the second patient side effects prohibited increasing the levels; the retinitis slowly progressed as the therapy was tapered because of severe neutropenia; off therapy the retinitis progressed rapidly. The third patient, on 17.5 mg/kg/week, had progression of macular retinal lesions without progression of peripheral lesions. Increasing the dosage to 25 mg/kg/week stabilised the macular lesions; neutropenia necessitated a decrease in dosage to 15 mg/kg/week, at which level, however, the retinitis did not progress further.

From review of the three series it appears that some patients could be maintained on low levels of drug without progression of the retinitis for extended periods while others developed reactivation even at higher levels of medication. The discrepancies must be due to variable resistance of the virus to the drug as well as to the varying degrees of immunodeficiency among the AIDS population.

In contrast to previous reports we observed in this series a higher incidence of patient toxicity to ganciclovir. Henderly *et al.* reported that three patients (13%) developed neutropenia (leucocytes $<1 \times 10^9/l$).¹⁹ Apart from one patient who developed dementia, no other side effects were reported.

Holland *et al.* noted that five of 14 patients (36%) developed reversible neutropenia requiring cessation of treatment,¹⁸ but no other side effects from therapy were observed.

Six of the seven patients in this study developed significant side effects from therapy. The side effects included a reversible, dose related neutropenia (five patients), thrombocytopenia (three patients), drug fever, and neuropathy. One patient was unable to complete the two-week induction therapy owing to significant neutropenia and thrombocytopenia. Five of the six patients on long term maintenance therapy required a reduction in dosage or transient withdrawal from the drug. Side effects such as neutropenia were reversible in this series with discontinuation of the medication or reduction in dosage. With close follow-up the therapy could often be restarted within seven to 14 days.

Side effects of ganciclovir therapy which have been described in previous series and which were not seen in our patients include increased serum liver enzymes, eosinophilia, nausea, myalgias, anorexia, disorientation, hallucinations, rash, and phlebitis.¹³ In this study a cilioretinal artery occlusion was observed in one patient while on therapy, which to our knowledge has not been previously reported. Patients with AIDS are considered to have immunological mechanisms which produce embolic phenomena or vascular occlusion. Therefore it is unknown whether the occlusion was disease or drug related.

When the ganciclovir was discontinued and could not be restarted within two weeks, careful examination of the retina revealed a rim of inflammation to recur at the margins of the lesions which had previously been cleared. However, no new satellite lesions were observed in previously uninfected retina. The fellow eyes which were free of retinitis did not develop new lesions during such short periods. If therapy could be promptly restarted at doses which had previously controlled the retinitis, then the retinitis was often again controlled. However, if longer than two weeks elapsed before restarting therapy, an increased dose of ganciclovir was often necessary to control the recurrence, and in some cases the increased dose which was required could not be tolerated, leading to progression and blindness.

Our results suggest that in some patients a cumulative weekly dose of 15 mg/kg/week of ganciclovir may be sufficient to control retinitis that has been stabilised by a higher induction dosage. In this report we have also shown that 25 mg/kg/week of ganciclovir can reverse a recrudescence of retinitis which may occur after interruption of therapy.

The efficacy of ganciclovir in clearing CMV from the blood, urine, and other previously culture-

positive sites has been clearly demonstrated in past studies.^{13,14} Only one of our patients who received a full induction course of therapy had virus recoverable from a body fluid. It is of note that this patient's vision and retinal inflammation improved despite concomitant viraemia. Conversely, several patients on maintenance therapy in this series were culture-negative despite progression of their eye disease. One patient had CMV cultured from a bronchial wash but not from blood or urine at the time of worsening retinitis. This may reflect the inability to achieve drug levels sufficient to control tissue infection, though the levels may be sufficient to clear the blood and urine of virus. While all patients with ocular disease consistent with CMV had blood or urine cultures that were initially positive, negative blood or urine cultures during therapy did not necessarily predict the clinical response.

In conclusion, this pilot study adds to the previous reports and demonstrates ganciclovir to be a promising long-term treatment for CMV retinitis in the AIDS patient. In our series the intravenous drug was used in an outpatient setting for over 30 weeks with stabilisation and often regression of retinal disease. In contrast to previous reports, ganciclovir produced side effects in a higher proportion of patients. The spectrum of ganciclovir toxicity in this report includes neutropenia, thrombocytopenia, drug fever, and neuropathy. The physician using ganciclovir must be familiar with and monitor carefully the varied manifestations of ganciclovir toxicity in order to adjust therapy effectively.

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Retinochoroiditis in acute Epstein-Barr virus infection

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SUMMARY The case is reported of a 17-year-old male with secondary glaucoma and retinochoroiditis complicating acute clinical infectious mononucleosis. The diagnosis was confirmed by Epstein-Barr virus specific serology. Toxoplasmic infection was initially suspected. The differential diagnosis and relevant literature are discussed.

A recent awareness of the role of the Epstein-Barr virus (EBV) in ophthalmic diseases exists.¹⁻⁵ We describe a patient which further substantiates this association.

Case report

A 17-year-old male presented with pain and blurred vision in the left eye. Three weeks previously he had had an influenza-like illness with sore throat and cervical lymphadenopathy. Oral erythromycin had been prescribed. Ten days later he developed a maculopapular rash on the trunk.

The visual acuity was 6/6 Snellen right and finger counting at 1/3 meter left. The right eye was white, with no evidence of anterior chamber activity. There were 1+ cells in the right vitreous cavity and a discrete area of active retinitis of less than 1 disc diameter centred on a retinal vessel superior to the macula. In the left eye there were 3+ external injection, corneal stromal oedema, multiple large keratic precipitates, a relative afferent pupil defect, 3+ anterior chamber cells, and intraocular pressure of 40 mm Hg by Goldman applanation tonometry. Koeppe iris nodules were present. There were 3+ cells in the vitreous cavity and a large area of active, white, fluffy retinitis with a fresh retinal haemorrhage in its centre at the posterior pole, with overlying vitreous haze (Fig. 1). Retinal vascular sheathing was present, with staining of vessel walls on fluorescein angiography. The left optic disc was oedematous. Systemic examination revealed a fading maculopapular rash on the trunk, cervical lymphadenopathy, and mild splenomegaly. Serum electrolytes and liver function tests were normal. There were 2%

atypical lymphocytes. Serological tests for syphilis and human immunodeficiency virus were negative. Serology (Table 1) confirmed acute EBV infection and prior toxoplasma infection. EBV serology was performed by conventional immunofluorescent staining,⁶ employing screening dilution of 1/8 for viral capsid antigen (VCA) and 1/2 for Epstein-Barr nuclear antigen (EBNA), and by peroxidase staining⁷ following the maker's protocol.

The patient was prescribed clindamycin 450 mg, prednisolone 60 mg, and acetazolamide 1 g daily by mouth initially. The prednisolone was reduced over a 10-day period. Dexamethasone 0.1% and mydriatic



Fig. 1 Left eye. Active retinochoroiditis with optic disc oedema seen through the vitreous haze.

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Table 1 Results of antibody studies

Serum antibody	Initial	One month	Eight months
Epstein-Barr viral capsid IgG	1/16	1/16	1/32
Epstein-Barr viral capsid IgM by fluorescent staining	Positive	Equivocal	Negative
Epstein-Barr viral capsid IgM by peroxidase staining*	Positive	Negative	Negative
Epstein-Barr nuclear antigen	Negative	NT	Positive
Rheumatoid factor	Negative	Negative	Negative
Paul-Bunnell test	≥1/14336	NT	NT
Paul-Bunnell after absorption with guinea pig antigen	≥1/14336	NT	NT
Ox cell antigen	≤1/7	NT	NT
Cytomegalovirus	≤1/16	≤1/16	NT
Herpes simplex	≤1/16	≤1/16	NT
Herpes varicella zoster	≤1/16	≤1/16	NT
Toxoplasma dye test	1/256	1/256	1/512
Toxoplasma IgM ELISA	Negative	Negative	Negative

NT=not tested. *Ipazyme True-IgM, Biological Industries Ltd, Cumbernauld, UK.

eye drops were instilled. The intraocular inflammatory signs abated rapidly and vision had recovered to 6/36 Snellen by day 7. A white, atrophic macular scar finally occurred, with surrounding pigmentation.

Discussion

EBV infection occurs in most young adults in developed countries, producing an infectious mononucleosis (IM) syndrome of fever, tonsillopharyngitis, and lymphadenopathy. Follicular conjunctivitis is the most common ocular manifestation of acute EBV infection.⁸ Keratitis and optic neuritis are also recognised.^{2,9} Aseptic meningitis, encephalitis, transverse myelitis, Guillain-Barré syndrome, and cranial nerve palsies are occasional neurological complications of acute EBV infection.¹⁰

The differential diagnosis of chorioretinitis of infectious aetiology includes cytomegalovirus (CMV), *Toxoplasma gondii*, herpes simplex and zoster virus, and syphilitic infections.¹¹ Despite the systemic clinical and haematological similarities of acute EBV infection and acquired CMV or *Toxoplasma gondii* infections, chorioretinitis is not an established manifestation of clinical EBV infections. Raymond *et al* recently described punctate outer retinitis in a child during a clinical episode of active EBV infection.⁵ There was no anterior uveal activity in that case. Toxoplasmic retinochoroiditis was initially suspected, as in our patient. Acquired systemic toxoplasma infection with associated retinitis is unusual and has been serologically excluded in our patient.^{12,13} A reactivation of a

previous toxoplasmic focus seems unlikely, as there were no old chorioretinal scars. Tiedeman described multifocal choroiditis with panuveitis in otherwise healthy patients who had serological evidence of recent or continuing chronic EBV infection, without acute IM-like illnesses.³ Bonamour and Pommier described acute chorioretinitis with a positive Paul-Bunnell result but did not include fundal photographs.¹⁴ Isolated case reports of retinal changes in association with IM exist^{15,16} but do not resemble the acute chorioretinitis of either Bonamour and Pommier's patient or ours.

Ophthalmologists need to consider EBV infection among the differential diagnoses of acute retinochoroiditis and request appropriate serological tests. Ocular manifestations of EBV infection may be more widespread than suspected.

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The Pulfrich phenomenon and its alleviation with a neutral density filter

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SUMMARY A case is described in which a presumed vascular accident resulted in long-standing visual difficulties in both reading and the analysis of vectors of moving objects. Clinical examination revealed minimal right optic atrophy with a relative superior altitudinal visual field defect associated with a positive Pulfrich effect. A partial head turn to the right in association with paresis of saccades and pursuit eye movements to the right was also evident. Spectacles for distance which incorporated a neutral density filter before the left eye were prescribed. These practically eliminated the Pulfrich effect and alleviated the problems of vector analysis. A near correction was provided which incorporated prisms with bases to the right. This eliminated the reading difficulties. The visual problems experienced by patients suffering from a positive Pulfrich effect are described and discussed.

The Pulfrich effect or stereophenomenon¹ is a disturbance in the perception of a moving object brought about by a difference in the time taken for the image data from each eye to be registered in the occipital cortex. When one or the other eye is covered by a neutral density filter, an object typically a pendulum bob, moving at right angles to the line of sight – that is, in the fronto-parallel plane (FPP) – appears to move in an elliptical path. The relative delay in perception for one eye creates slightly different apparent locations in space for the images from each eye. This difference is registered cortically as a geometric disparity which results in an incorrect analysis of the vector, giving the illusion the striking characteristic of apparent depth.

The phenomenon can either be elicited in normal observers by placing a neutral density filter in front of one eye (provoked Pulfrich effect), or occur as a result of pathological disturbance in optic nerve function (positive or spontaneous Pulfrich effect). The elliptical path of the pendulum appears clockwise when the filter is placed before the left eye and anticlockwise for the right eye (Fig. 1). The magnitude of the effect (that is the apparent size of the minor axis of the ellipse) is proportional to the density of filter used. The effect occurs independently

of eye movements, and for the provoked effect the eyes track the actual rather than the apparent path of the pendulum.²

Emphasis has been given to the diagnostic value of the test, which investigates the effect in patients with optic nerve dysfunction,^{3,9} but little attention has been directed to the problems experienced by patients and whether or not these can be alleviated. We describe a patient whose symptoms of visual disturbance due to the Pulfrich effect were ameliorated by using a suitable filter before the unaffected eye, and for whom the prescription of appropriate prisms overcame reading difficulties due to paresis of saccadic and pursuit eye movements to the right.

Case report

The patient, born on 6 December 1937, was a housewife who was first seen by one of us (GD) in December 1984. Three years earlier she had undergone surgery to the temporomandibular joint under general anaesthesia. She had woken from surgery with weakness of the right arm and leg, right upper motor neurone facial palsy, difficulty in looking to the right, right upper quadrant homonymous visual field loss, and impairment in vision of the right eye. However, there was no gaze evoked nystagmus, no lateropulsion could be elicited, and 'Doll's head' eye

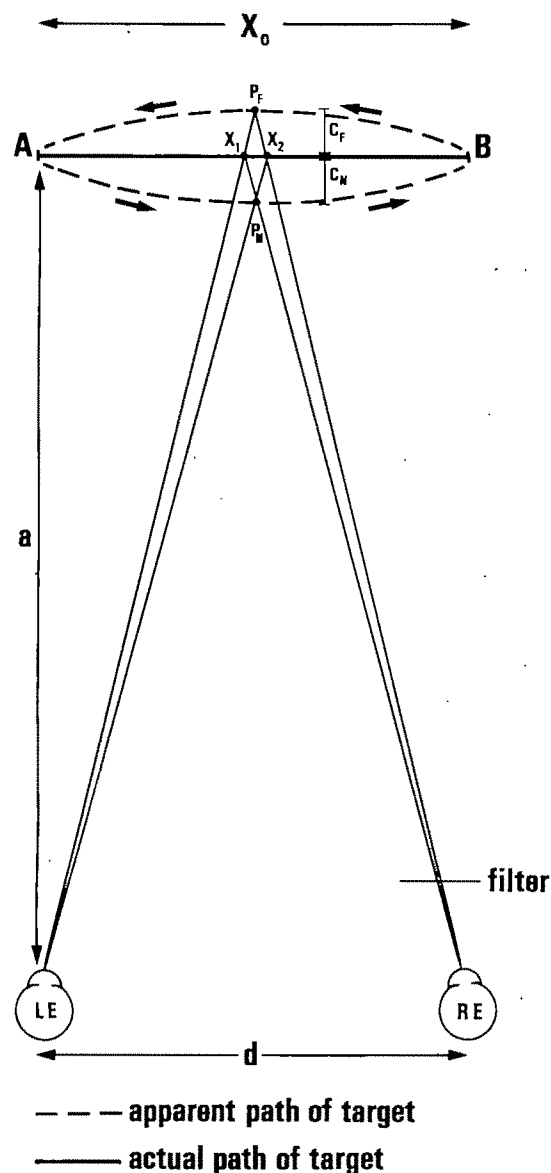


Fig. 1. The provoked Pulfrich effect: diagram of the apparent path of target moving with a simple harmonic motion along the plane AB, when a filter is placed before the right eye.

movements were normal. These symptoms and signs were attributed at the time to multifocal vascular accidents affecting the left cerebral hemisphere and the right optic nerve, which had followed a hypotensive episode during surgery. During the ensuing six months her limb and facial weakness and her homonymous field defect resolved spontaneously,

but a subtle relative superior altitudinal visual field defect was still detectable for the right eye by Tübinger perimetry (1.0 W, 100 Abs).

On presentation in 1984 the patient complained of two anomalies of her visuospatial environment, from which she had suffered from the time of her operation. Objects moving towards her from the right side appeared to swerve to approach her directly; she also experienced great difficulty in placing objects centrally, always placing them to her left.

When she was a passenger in a car on the motorway, cars on the opposite carriageway appeared to jump the crash barrier and approach her. Her most dramatic observation concerned her perception of a mechanical digger, which was moving in a field on her right while she was travelling in a car. As the car drove past, the digger appeared about to crash into the car and she took evasive action, pushing the driver to one side. The apparent height of doorways was also underestimated, and she felt that she had to duck her head when moving between rooms at home. Activities requiring near central vision were particularly difficult. Reading material was placed to the left for greatest clarity and she had abandoned embroidery, as she was unable to keep her stitches in line.

On examination she preferred to adopt a head turn to the right. Her corrected visual acuities were 6/9 right (+0.50/+0.25 at 170) and 6/6 left (+0.25/+0.25 at 170). Examination of her eye movements revealed an impairment of both saccades and pursuits to the right; eye movements to the left were full and normal.

There was pallor of her right optic nerve head in association with the persistent right relative superior altitudinal visual field defect. Despite careful testing there was no clinically detectable afferent pupil deficit, and the pupil cycle time¹⁰ for three separate recordings for each eye was 0.72, 0.70, and 0.72 s right and 0.72, 0.74, and 0.72 s left. A pendulum was employed to elicit a Pulfrich phenomenon, and this was positive, the pendulum bob appearing to rotate in an anticlockwise fashion. Third generation computerised tomography did not demonstrate any intracerebral or optic nerve pathology. Pattern reversal visual evoked responses with 1.8° check size gave latencies of 95±5 ms for each eye, with equal amplitudes of approximately 75% of the normal for our laboratory.

CLINICAL METHODS*

A +2.50 DS addition to each eye gave a combined near visual acuity of N12. Additional 6-dioptre

*Informed consent was gained from the patient for all the procedures described.

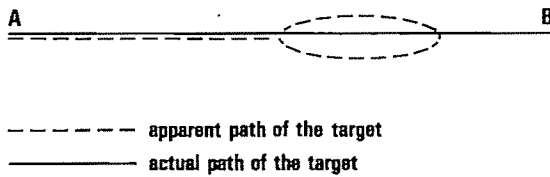


Fig. 2. The appearance of the target with a 0.2 ND filter placed before the left eye. The elliptical pattern of the spontaneous Pulfrich effect remained as a very shallow ellipse as the target moved into the right field and a straight line as the target moved out to the left field.

prisms with bases to her right improved her near acuity to N6, and also enabled the patient to hold reading material in the central position. Spectacles with this prescription were dispensed; these allowed her to read with ease and to perform embroidery accurately.

The Pulfrich phenomenon was initially investigated by a white target mounted on a metronome. The target appeared to move in an asymmetrical anticlockwise ellipse which was shallower when the target moved from right to left and was seen to be higher on the right than the left. The apparent FPP traversed by the target also appeared to tilt, being nearer on the right limit of excursion and further away on the left. A 0.3 neutral density (ND) filter placed before the left eye reversed the effect, and a 0.2 ND filter partially eliminated it. With the latter filter no ellipse was seen for target positions to her left, but a shallow ellipse was still present, but not tilted, for target positions to her right (Fig. 2). The 0.2 ND filter was initially taped to the left lens of the distance spectacles, and subsequently replaced by an ophthalmic tint (Norvac G33, Norville Optical) which was empirically selected on the basis of elimination of the Pulfrich effect. The luminous transmission factor of this ophthalmic tint was found to be slightly greater than a 0.2 ND filter.

When reviewed three months later the patient had found that the distance glasses had reduced the strange patterns of perception for both moving and for stationary objects. The filter was not required for near, since the illusion was experienced for distance targets only. This effect has been sustained for the ensuing three years. The patient has not noted the minor shifts in colour vision reported with prolonged use of a neutral filter¹¹ and neither has there been any evidence of visual fatigue.¹²

Discussion

Although the visual evoked response (VER) had shown no difference in latency between the two eyes, the presence of the positive Pulfrich effect, which was

reproducible, suggested that a small latency difference beyond the limits of detection by the VER was present. The magnitude of the Pulfrich effect was determined using an X-Y plotter modified so that its pen carriage would transcribe an ellipse as it traversed the X axis. The size of the ellipse (minor axis) could be varied, and a 12 mm white disc target was used, supported 20 cm above the pen carriage. The patient was asked to observe the target without spectacles, and the apparatus was adjusted until the target transcribed an ellipse which was not observed by the patient. Lit¹³ has given the equation which describes the time difference (Δt) of a target to travel from X_1 to X_2 along the FPP. This is equal to the difference in the latency periods between the two eyes (Fig. 1).

$$\Delta t = \frac{T(X_1 - X_2) \times 1000}{2\pi X_0}$$

$$\text{where } (X_1 - X_2) = \frac{dC_n}{a - C_n} \text{ or } \frac{dC_r}{a + C_r}$$

T is the period and X_0 is the amplitude of the pendulum. For the arrangement described above, the ellipse which eliminated the Pulfrich effect had an amplitude of 16.5 cm, a period of 3 seconds, and a

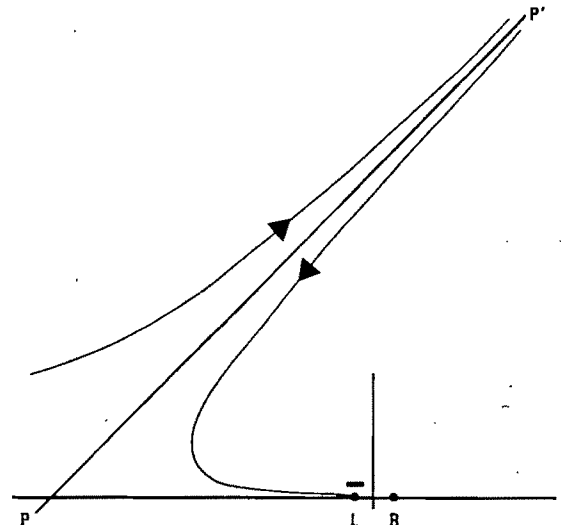


Fig. 3. Theoretical hyperbolas which describe the apparent path of a moving object along plane PP' , for the Pulfrich effect provoked by a filter before the left eye. For object moving from left to right the path is described by the hyperbola above the plane (rightwards pointing arrow) and for objects moving from the right to left along PP' the apparent path is along the hyperbola below the plane (leftwards pointing arrow). Redrawn from Spiegel¹⁴ and reproduced with permission.

minor axis of 2.38 cm when viewed from 1 metre. These figures result in a latency difference (Δt) of 2.25 milliseconds. This value is outside the range of detectable latency difference for the VER.

Although it has been suggested previously that a neutral density filter would abolish the symptoms engendered by the Pulfrich effect, we are aware of only a single case in which this has been attempted. This was the first recorded case, but no follow-up was reported.¹⁴ Many of the bizarre symptoms that our patient reported have been recorded in previous studies on patients with demyelinating disease^{3,6,8} and have been replicated by experimental studies of the provoked Pulfrich effect in normal individuals.^{6,15} However, for an object moving in a straight path which obliquely intersects the interpupillary plane the apparent path has been shown theoretically to be hyperbolic (Fig. 3). Various hyperbolas are observed depending on the angle of intersection and whether the target approaches or recedes from the observer.¹⁶ This may explain our patient's localisation of moving objects (such as cars), and might also relate directly to her perception of doorways, in which the height was underestimated. In this case the object is stationary, and it is the observer who is moving. In addition the phenomenon of irradiation stereoscopy¹⁷ may be the reason that patients with a spontaneous Pulfrich effect notice that static objects appear tilted. However, brightly lit high reflectance objects are needed to produce the effect in the laboratory; hence the influence of irradiation stereoscopy in this case is uncertain.

Increased latency of the pattern reversal VER occurs in cases of optic neuritis.¹⁸ In a detailed study Rushton¹⁹ has compared this with the delays determined from the associated Pulfrich effect. Although the presence of a Pulfrich effect correlated well with the detection of increased latency, there was no correlation between the latency values determined by the two methods. Rushton suggests that this may have been due to small tracking variations as patients followed the moving target, since foveal and non-foveal locations have differing latencies. This may have occurred with our patient, since the residual ellipse observed by her when the neutral density filter was in place was seen on right gaze, the direction of the gaze paresis.

We presume that a multifocal ischaemic episode caused the symptoms and signs. The relative hemiparesis and facial palsy could be accounted for on the basis of a vascular lesion in the contralateral basal pontine region. This could also have affected the pontine paramedian reticular formation and thus given rise to the permanent dysfunction in horizontal gaze. In addition, impaired vision of the right eye implicates right optic nerve dysfunction, thus

implicating the internal carotid artery system. However, lesions in the medulla oblongata can be discounted, since there are no symptoms consistent with those typically encountered in Wallenberg's Syndrome,²⁰ namely lateropulsion, imbalance, and tilting of the visual world.

The symptoms of anomalous perception described by our patient can easily be ignored or dismissed if the clinician is unaware of the Pulfrich phenomenon. The condition can be both disturbing and disabling. This case highlights the problems which such patients experience and demonstrates that an appropriate neutral density filter before the least affected eye can bring considerable long-term symptomatic relief.

We gratefully acknowledge the assistance given by colleagues in these investigations. R G Ackerley, J R Pugh, and A S Eadie assisted with the generation of ellipses on the XY plotter and with the recording of eye movements. D Allan recorded the VER and eye movements at the Western Infirmary, Glasgow.

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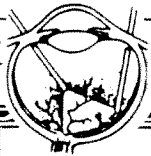
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Clearing of corneal argyrosis by YAG laser

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From the Department of Ophthalmology, Ichilov Hospital, Tel Aviv, Israel

SUMMARY A 75-year-old woman with corneal argyrosis was treated by a Q-switched Nd-YAG laser iridotomy after acute angle closure glaucoma. Each laser shot caused clearance of the argyrotic deposits anterior to the iridotomy site. The same effect was seen when a preventive iridotomy was performed in the other eye. The areas of clear cornea remained unchanged for a follow-up period of eight months.

Corneal argyrosis is the deposition of silver granules in the deep stroma and Descemet's membrane following the use of topical silver nitrate.¹ The cornea takes on a grey appearance by reflected light. The deposition is considered to be permanent, and no efficient method of removal has been reported.

Case report

A 75-year-old woman was admitted to our department because of an acute attack of angle closure glaucoma in her right eye. On examination we found the typical bluish grey pigmentation of the conjunctiva, particularly in the lower fornix, and the grey colour of the deep cornea which are characteristic of argyrosis. The patient recalled having received extensive silver nitrate therapy for trachoma 50 years previously.

After the acute attack had been arrested medically a laser iridotomy was performed with a Q-switched Nd-YAG laser (Lasag). A single burst of 10 mJ through an iris contact lens was used with the helium-neon beam focused carefully on the iris. Multiple shots were necessary to achieve an iridotomy. To our surprise each laser shot caused a bubble in the deep

cornea, with disappearance of the argyrotic deposit immediately anterior to the iridotomy site. Each window of clear cornea had an oval shape and was slightly larger in area than the iridotomy (Fig. 1). The same effect was seen when a preventive iridotomy was performed in the patient's left eye. The areas of clear cornea remained unchanged for the follow-up period of eight months.

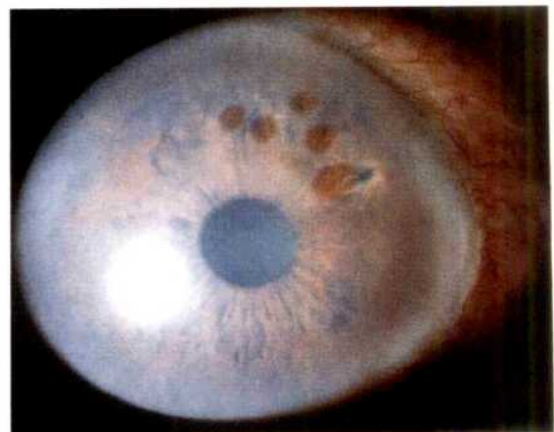


Fig. 1 Clear areas in argyrotic cornea after YAG laser treatment.

Correspondence to O Geyer, MD, Department of Ophthalmology, Ichilov Hospital, 6 Weizman Street, Tel Aviv 64239, Israel.

Discussion

To the best of our knowledge the clearing of silver deposits in the cornea with YAG laser has not been previously reported. It is most probably due to partial absorption of the laser beam by the silver deposits causing their optical breakdown and vapourisation. This was evidenced by bubble formation in the deep cornea with each laser shot.

Because corneal argyrosis is a rare finding today we do not expect the YAG laser to have any clinical use

in its treatment. However, perhaps this finding can serve as a basis for using YAG laser in attempts to clear other precipitations and pigmentations in the cornea, such as blood staining, which are much more common.

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Case of cerebrotendinous xanthomatosis. I: Unusual ophthalmic features

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SUMMARY A case of cerebrotendinous xanthomatosis is reported. In addition to the classical ophthalmic and systemic features the patient presented with unilateral proptosis. This feature has never previously been reported. The results of investigations are described and illustrated.

Cerebrotendinous xanthomatosis (CTX) is a rare metabolic disease of autosomal recessive inheritance.¹ As a result of a defect in bile acid synthesis there is an accumulation of cholestanol, the 5-dihydro derivative of cholesterol, in serum and tissues.^{2,3}

The clinical signs include bulky tendon xanthomata, neurological dysfunction, spinal cord paresis, premature coronary atheroma, and early onset cataracts.⁴ There are indications that some of the more serious neurological manifestations are reversible with treatment.^{5,6}

This report is only the second in literature of the UK⁷ and describes a new ophthalmic symptom – proptosis due to orbital involvement. From our experience CTX may occasionally go unrecognised.

Case report

A 42-year-old single unemployed labourer presented in February 1986 complaining of deteriorating vision. His vision was said to have always been poor. His optician reported a best corrected acuity of 6/18 in each eye at age 21, when he was first prescribed spectacles. In 1979 and 1981 tendon lumps had been excised (notes not traceable). The family history was negative for xanthomata, hyperlipidaemia, and consanguinity.

On general examination he was of short stature with brachydactyly and dolichocephaly, and had

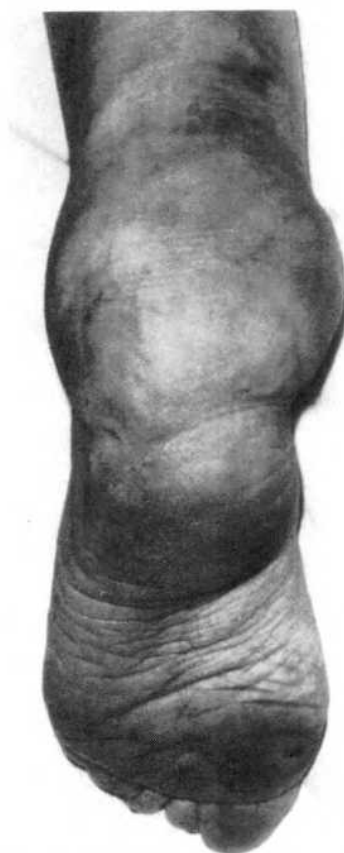


Fig. 1 Bulky xanthoma of left Achilles tendon.

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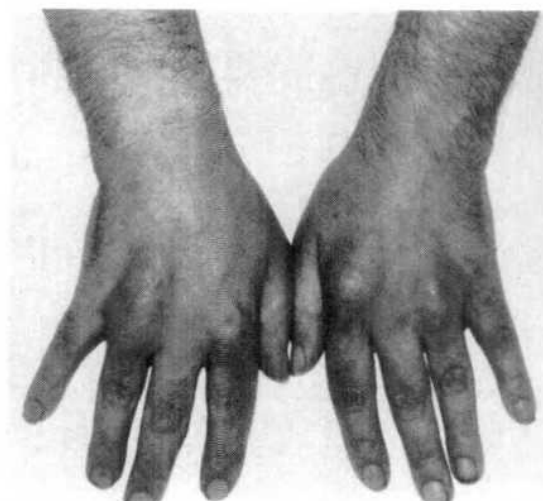


Fig. 2 Brachydactyly with extensor tendon xanthomata of hands.

multiple bulky xanthomata of the extensor tendons, notably on his elbows, hands, and Achilles tendons (Figs. 1, 2). Ophthalmic examination showed best corrected visual acuities of right 2/60 and left 4/60. He had bilateral coronary nuclear and posterior subcapsular cataracts (Fig. 3).

In May 1986 he underwent right extracapsular cataract extraction with insertion of a posterior chamber intraocular lens. He made an uneventful recovery. Best corrected acuity was 6/6 part and the right fundus was normal. In August 1986 the tendon xanthoma on his left elbow was excised. Histological examination showed a tuberos xanthoma.

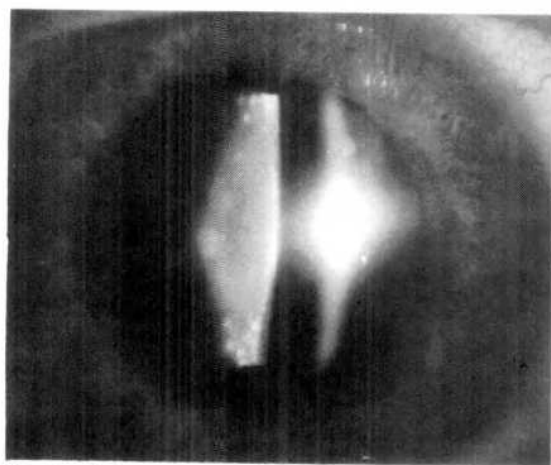


Fig. 3 Slit-lamp photograph of left eye showing coronary and posterior subcapsular lens opacities.



Fig. 4 Left proptosis with mass in upper palpebral sulcus.

In October 1986 he presented with left proptosis. His visual acuities were right 6/9 and left counting fingers. There was a 2 mm left proptosis with a firm mass palpable in the upper palpebral sulcus (Fig. 4). Pupils and eye movements were normal. A-scan ultrasonography showed a well demarcated lesion close to the superior aspect of the left globe, non-compressible, and of low reflectivity. CT scans of the left orbit revealed a marked concentric thickening of the left levator complex (Figs. 5 a,b,c). Biopsy of the lesion under local anaesthetic showed a typical xanthoma. The proptosis remained unchanged.

In September 1987 he underwent left extracapsular cataract extraction with insertion of a posterior chamber intraocular lens. After the operation his recovery was uneventful, with a best corrected acuity of 6/5. The left fundus was normal. On this occasion the lens anterior capsule, nucleus, and cortical washings were collected and preserved in liquid nitrogen for biochemical analysis.

A year later his visual acuities were 6/6 part right, 6/6 left, and N5 for near vision.

BIOCHEMICAL INVESTIGATIONS AND TREATMENT

Before treatment was begun serum lipid analysis was performed. The results were: fasting cholesterol 6.1 mmol/l (reference range 2.8–7.2); fasting triglycerides 1.6 mmol/l (0.8–2.0); HDL-cholesterol 0.9 mmol/l (1.0–1.5); serum cholestanol 93 µmol/l (<10).

The plasma biochemical profile, including liver function tests, was normal. Treatment was begun with ursodeoxycholic acid, increasing gradually to 600 mg per day. After eight months' treatment there had been no measurable change in the size of the xanthomata of the Achilles tendon, though the left proptosis had slightly regressed. The patient admitted poor compliance with therapy. His serial serum cholestanol levels remained elevated. Chenodeoxycholic acid has been shown to lower serum cholestanol levels and reverse neurological dysfunction in CTX^a but not xanthomata or cataracts. Our

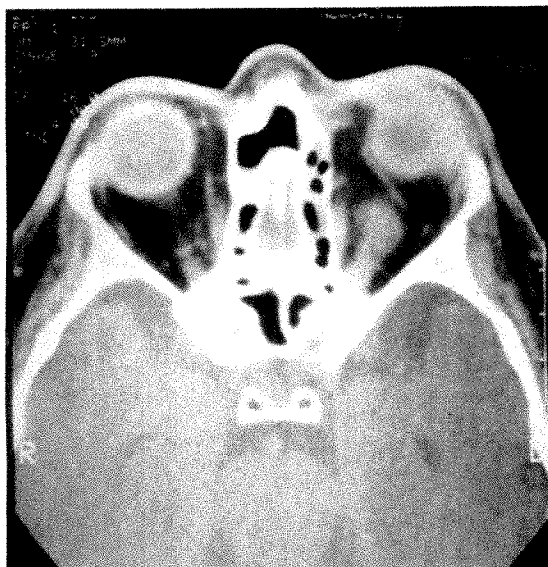


Fig. 5A

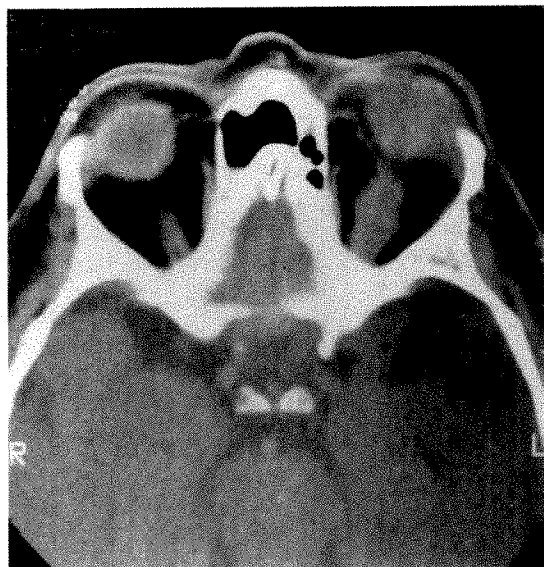


Fig. 5B

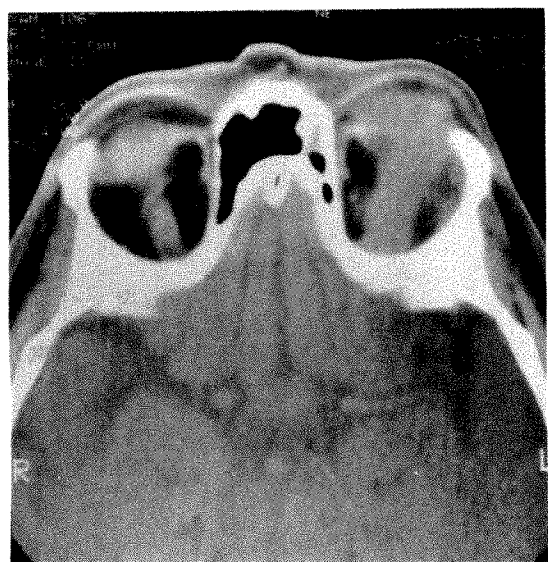


Fig. 5C

Fig. 5 Orbital CT scans showing mass in left levator complex.

patient's treatment has now been appropriately modified.

Discussion

Our patient shows clinical and biochemical features pathognomonic of CTX.² Cataracts, which may be

seen as early as age 15,¹⁴ have been recorded in about 85% of all reported cases. It is stated that cataract extraction 'by young adulthood' is usually necessary. Our patient's late presentation accounts for his relatively advanced age at surgery.

The typical lens opacity is described as 'zonular cortical' and is well illustrated in a recent review.² Our patient's opacities were more advanced than this.

We have found references to only three other ophthalmic complications in CTX, namely, xanthelasma deposition,¹ an increased content of sterols in the extraocular muscles,¹ and 'atrophy of the entire optic pathway'.¹⁵ Proptosis, however, is a hitherto undescribed clinical feature. In this case it is due to xanthoma deposition in the extraocular muscles and reflects the generalised tendency to xanthoma deposition, particularly in tendons, which affects the Achilles tendon most frequently but also the tibial tuberosities, triceps, and finger extensors.¹

If untreated, CTX leads to an unpleasant early death from relentless neurological deterioration with spasticity, ataxia, bulbar palsy, incontinence, and dementia.¹ Psychiatric disorders may be prominent.² Myocardial infarction may occur and has been recorded as young as age 36.¹⁶ The prospect of halting or even reversing this decline by treatment with oral bile acid supplements makes it vitally important that this condition be promptly diagnosed.

Treatment with chenodeoxycholic acid is reported to have resulted in a favourable biochemical response, with return of plasma cholestanol levels nearly to normal.¹⁷ Our patient was initially treated

with ursodeoxycholic acid because it has a lower reported incidence of gastrointestinal side effects.¹⁰ Failure of the biochemical abnormality to respond to ursodeoxycholic acid has been reported^{11,12} and is confirmed by our observations.

The mechanism of cataract formation in CTX is of some interest in view of the abnormalities of lipid metabolism in this disease. We have shown that there is a raised level of cholestanol in the cataractous lens in CTX compared with senile cataract (report in preparation). However, we have now demonstrated that CTX must also be included in the differential diagnosis of proptosis.

Our thanks are due to Mr Derek Mitchell, top grade biochemist, Department of Chemical Pathology and Metabolic Disorders, St Thomas's Hospital, London, for help with blood lipid analysis, and to Mr Ken MacLean, medical photographer, Royal Victoria Infirmary and General Hospital, Newcastle upon Tyne, for the clinical photographs. Copyright for the clinical photographs is held by the University of Newcastle upon Tyne.

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Ocular myasthenia gravis after D-penicillamine administration

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SUMMARY A 68-year-old black woman who was put on D-penicillamine therapy (250–500 mg per day, total dose 15 g) for rheumatoid arthritis developed ocular myasthenia gravis. Two weeks after she discontinued D-penicillamine her signs and symptoms cleared with no other treatment. Review of previous cases and possible immunological mechanisms are discussed.

D-Penicillamine is an invaluable therapeutic agent in a variety of illnesses. It is an amino acid that is a pyridoxine antagonist produced by hydrolysis of penicillin.¹ Beneficial use has been made of its chelating properties in metallic toxic states whether exogenous² (lead or mercury poisoning) or endogenous³ (Wilson's disease). Since combination with cysteine yields a more soluble complex, it is potentially useful in cystinuria.⁴ It has been used in rheumatoid arthritis,^{5,6} progressive systemic sclerosis,⁷ primary biliary cirrhosis,⁸ and haemophilic arthritis.⁹ With increasing long-term use of D-penicillamine, immune mediated disorders such as myasthenia gravis,^{10,25} polymyositis,²⁶ systemic lupus erythematosus,²⁷ pemphigus,²⁸ and Goodpasture's syndrome²⁹ have occurred. This case report provides an illustrative example of reversible myasthenia gravis related to D-penicillamine therapy.

Case report

The patient was a 68-year-old black woman who had had rheumatoid arthritis for 30 years. After four months of D-penicillamine therapy (250–500 mg/day for a total dose of 15 g she noticed the onset of diplopia and right ptosis, which increased in severity at night. No other muscular weakness was noted.

On examination a right ptosis was observed, with

palpebral fissures in primary gaze measuring 5 mm on the right and 10 mm on the left. In primary gaze a left hypertropia of 20 prism diopters was recorded. Prolonged upward gaze for two minutes yielded a positive fatigue test with increasing droop of the right upper eyelid. Cogan's lid twitch sign was also present. Her vision was 20/20 in both eyes. Her pupils, visual fields, slit-lamp appearances, and fundus were normal. Further neurological evaluation revealed no other focal or diffuse neuromuscular difficulty. A Tensilon (edrophonium) test was positive. Computerised axial tomography and lumbar puncture gave normal results. Laboratory tests gave normal values for thyroid function indices (T4-RIA, T3 uptake, TSH), serum vitamin B₁₂ and folate levels, and cerebrospinal fluid protein and glucose. The fasting blood glucose was 9.4 mmol/l (170 mg/100 ml). Complete blood count yielded a packed cell volume of 51% and a white cell count of $4 \times 10^9/l$, with a normal differential count. No antibody to acetylcholine receptor was detected in her serum. Ten days after cessation of D-penicillamine signs and symptoms cleared. The patient never required anticholinesterase therapy.

Discussion

Several drugs may produce a myasthenia gravis-like state (Table 1).³⁰ Since 1975, 10 case reports of 34 patients have strongly suggested an association between D-penicillamine and myasthenic gravis (Table 2). Patients with one of three underlying

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Table 1 Drugs inducing myasthenia gravis

Antibiotics	Colistin	Neomycin
	Gentamicin	Polymyxin
	Kanamycin	Streptomycin
Cardiovascular	Oxprenolol	
	Practolol	
	Trimethaphan	
Anticonvulsants	Phenytoin	
	Trimethadione	
Others	Tetanus antitoxin	
	Oral contraceptives	
	D-Penicillamine	

diseases – rheumatoid arthritis (31 patients), Wilson's disease (two patients), and progressive systemic sclerosis (one patient) – underwent treatment with D-penicillamine and developed ocular myasthenia. Ptosis and diplopia were present in all cases in which symptoms and signs were reported. Serum globulin assay in more than 75% of those cases that were tested showed an acute, usually transient, elevation of antibodies to acetylcholine receptors^{11 14 16 21 24 31 33} and, in another report, to striated muscle.¹¹ Electromyographic tracing of the muscle response to double-step stimulation showed the typical myasthenia decremental response on repetitive nerve stimulation.³⁴

The differentiation of drug induced from spontaneous myasthenia gravis is usually on clinical grounds. In the drug induced type the onset of symptoms is usually six to seven months after starting therapy but ranges from less than one month to eight years. Muscular weakness usually resolves two to three

months after stopping D-penicillamine, but recovery may occur after only several weeks or up to several years. It has been noted that two patients with myasthenia gravis induced by D-penicillamine had the HLA-DRI antigen in contrast to patients with idiopathic myasthenias, who typically have HLA-DR3 antigen.³⁴ This difference suggests a different genetic background, that these are two distinct populations, and that the drug induced myasthenias are not simply unmasked from a susceptible stage. Moreover, recurrence after discontinuing D-penicillamine has been reported.^{10 31} Usually a concomitant improvement in electromyographic tracings²⁵ and a decline in antiacetylcholine receptor antibodies^{21 24 25 30} are observed during clinical recovery, though the antibodies may remain raised.³² Some patients may require oral anticholinesterase treatment. Rarely, plasmapheresis may be necessary for short-term maintenance.¹²

The pathogenesis of drug-induced myasthenia gravis is not clear. D-Penicillamine has no direct effect on cell membrane miniature end plate potential,³⁰ amplitude, or ocular potential.³⁴ The increase in serum antibodies to acetylcholine receptors, as in primary myasthenia gravis,³⁵ implies a common pathogenesis. However, there are patients on D-penicillamine therapy who never develop antibodies³⁰ and there are also those who have antibodies but no myasthenic weakness.¹¹ Current theories on the mechanism of drug induced myasthenia gravis focus on altered immunological reactivity. A population of B cell lymphocytes has apparently been induced to manufacture antibodies to the acetyl-

Table 2 Review of literature: myasthenia gravis following D-penicillamine treatment

Author	Year	No of Patients	Underlying disease	Duration of treatment (months)	Time of recovery (months)	Antibody to acetylcholine receptor	Ocular myasthenia
Bucknall <i>et al.</i> ¹⁶	1975	4	RA	4,5,8,9	1.1–1/3.NA.NA	NA	+
Czlonkowski ¹⁹	1975	1	W	13	1–1/2	NA	+
Masters <i>et al.</i> ¹¹	1977	8/1 (9)	RA/W	NA/100	NA/NA	4+,1–/+	NA/+
Gordon and Burnside ¹⁹	1977	1	RA	4	7	NA	+
François <i>et al.</i> ²⁶	1978	1	RA	5	3	NA	+
Russell and Lindstrom ²¹	1978	1	RA	2	8	+	+
Atcheson and Ward ¹¹	1978	1	RA	1/15	1	–	+
Vincent <i>et al.</i> ¹¹	1978	3	RA	6,20,9	NA	3+	+
Sundstrom and Schuna ¹⁷	1979	2	RA	6,7	2 26 mo.	NA	+
Keesey and Novom ¹⁷	1979	1	RA	9	8	+	+
Argov <i>et al.</i> ¹¹	1980	2	RA	10,18	NA	+	+
Rousseau and Diendonno ¹¹	1980	1	RA	6	2	+	+
Albers <i>et al.</i> ¹⁴	1980	1	RA	7	6	+	+
Torres <i>et al.</i> ¹⁶	1980	1	PSS	6	10 mo.	+	+
Bocanegra <i>et al.</i> ¹⁹	1980	1	RA	3	2+	–	+
Lang <i>et al.</i> ¹²	1980	2	RA	6,7	6,6	1+1–	+
O'Keefe <i>et al.</i> ²⁴	1985	2	RA	9,36	4,4+	+/+	+

RA=rheumatoid arthritis. W=Wilson's disease. PSS=progressive systemic sclerosis. NA=not available.

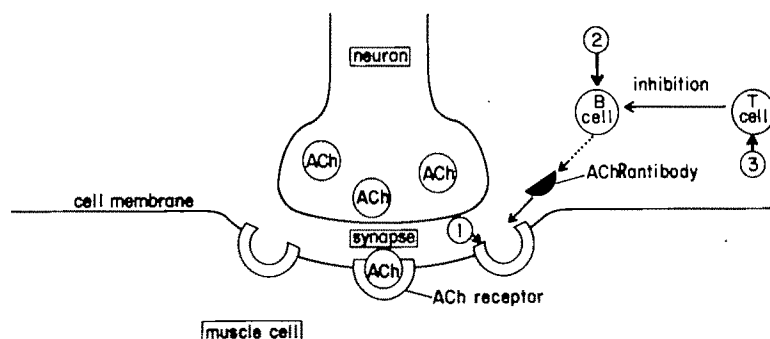


Fig. 1 Possible sites of penicillamine action: (1) Alteration of acetylcholine receptor. (2) Stimulation of B cell lymphocytes. (3) Inhibition of suppressor T cell lymphocytes.

choline receptors. This could be the result of several possibilities. (Fig. 1): (1) Acetylcholine receptor antigenic properties are altered, which would make self recognition more difficult.³⁶ (2) There is a loss of suppressor T cell control over B cell production of antibodies. In-vitro studies demonstrate that D-penicillamine decreases T cell division.³⁷ (3) Direct stimulation of B cells, specific or non-specific, which would lead to increased levels of antibodies.

Although D-penicillamine has been extensively used for several disease states, most patients who develop myasthenia gravis are those with autoimmune disease, suggesting an inherent susceptibility to D-penicillamine. For example patients with rheumatoid arthritis have demonstrable defects in suppressor T cell function.³⁸

An alternative explanation, not based on an immunological model, is that D-penicillamine stimulates prostaglandin E_1 synthetase to produce prostaglandin E_1 , which occupies an allosteric site on the acetylcholine receptors.³⁹ This may alter acetylcholine coupling with receptors.

With increasing use of D-penicillamine more patients will undoubtedly present with drug induced secondary myasthenia gravis. Since ocular features are predominant, ophthalmologists should bear in mind the association of myasthenia gravis with D-penicillamine.

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Correspondence

Monocular infantile cataract, intraocular lenses, and amblyopia

SIR, We welcome your invitation to reply to the editorial comment on our article,¹ as we consider Mr David Taylor overstates the case against intraocular lens implantation.²

We do not differ on the management of the majority of children presenting with cataract, and are equally aware that amblyopia is the dominant factor in their management and prognosis. We agree that on present knowledge patients with dense unilateral cataract known to be present from birth must be treated very early indeed to have any hope of a good visual outcome; in such patients presenting later we do not advise surgery. There is, however, a significant minority of cases where the duration of visually significant cataract is uncertain, who may have had a period of early binocular experience. This is especially recognised in patients with posterior lenticonus, and such patients contribute to the high mean age at surgery of our non-traumatic cases.

We endorse Mr Taylor's anxieties about excessive amblyopia treatment. Prolonged periods of occlusion and associated poor vision, allied with the stress of contact lens therapy, may be a strongly negative factor at a critical stage in the child's general development. Such treatment can be justified only if there is reasonable hope of significant benefit. In our series a number of the poor visual results occurred in patients with poor compliance or poor response to occlusion during contact lens wear. In such situations we did not consider it appropriate to continue to subject patients to contact lens wear, considering it a better option to implant an intraocular lens and revert to minimal occlusion in the hope of preserving peripheral visual function. We would stress that in patients untreated or left without correction after surgery, for example by failure to wear contact lenses, the final corrected acuity may be light perception only.³

Ophthalmologists are familiar with the amblyope who acquires a blinding disease in the good eye. Tömmila and Tarkkanen⁴ estimated the incidence of loss of vision in the healthy eye of amblyopes to be 1.75 (SD 0.30)/1000 in Finland. For the same period the overall blindness rate in children was 0.11/1000 and in adults 0.66/1000 of the general population. They infer that the risk of becoming blind is considerably higher for the amblyope than for the general population and the value of retaining vision in patients with unilateral cataract should at minimum be considered in this context. It is also in this context that we comment, 'even an acuity of 1/60 represents a significant improvement (above light projection) for a reserve eye'. We do not imply that this is an acceptable target acuity, and indeed only two patients in our series had final acuities as poor as this.

We re-emphasise that the patients in our report are a group selected for intraocular lens implantation because they were considered unsuitable for, or failed with, conventional treatment. We share Mr Taylor's anxiety over the long-term stability of intraocular implants. However, our own and others' experience, and experience with adults,

indicates that in the medium term these implants are stable. The techniques available to deal with complications continue to improve, but at present there is no treatment available for late severe amblyopia. We therefore consider that amblyopia management should take precedence, and in that respect do not consider the possibility of late implant complications to be an 'all important risk'.

Even in centres specialising in the contact lens treatment of paediatric aphakia up to 15% of children are considered primary contact lens failures,⁵ and complications are not infrequent.⁶ Alternative means of optical correction are required for this by no means insignificant minority. We consider our findings support the view that intraocular lenses are one of the options to be considered. Mr Taylor argues untreated unilateral cataract to be of minor significance to a child's life, only an acuity compatible with a normal education to be of any value for a 'reserve eye', and intraocular lenses 'never likely' to be an ethical option in children. We must continue to disagree on all these points.

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Book review

Retinal Detachment: Diagnosis and Management. 2nd edn. By WILLIAM EDMUNDS BENSON. Pp. 238. £36.00. Lippincott: Philadelphia, 1988.

In the second edition of this book Dr Benson has continued the concise style and presentation that characterised the first edition. The book is intended, as the author states in his preface, to provide residents, fellows, and practitioners of ophthalmology with a guide to the diagnosis and management of retinal detachment. In the presentation of the

second edition these objectives have been kept firmly in the author's mind, and the result has been successful. There are 11 chapters dealing with various aspects of retinal detachment. Anybody who has attempted to write a short textbook on retinal detachment will know that the main difficulty is to decide not only what to include and what to leave out, but also in what order to present the information. Thus Dr Benson chooses to leave the examination of the retina until chapter 6, in which he gives many useful tips on examination.

In the chapter on basic surgical technique the author describes most of the techniques currently in practice, though few surgeons would appear now to be using diathermy for conventional retinal detachment surgery, and scleral dissection of any sort is rather unusual. The last chapter is given over to new techniques of the treatment of retinal detachment. Here the author deals with topics that are at present controversial. It is interesting to have this chapter included in the book, and it also acknowledges that these areas are likely to be a source of change in the years ahead. In the appendix the author has included some examples of retinal detachment and suggested methods of treatment. This is a very helpful way for the beginner to check the approach to a variety of problems.

Although the book is not about pars plana vitrectomy, the author might have made clearer the situations where he considers that retinal detachment surgery is best treated by this procedure. To save expense colour has been used sparingly throughout the book, and consequently many of the diagrams are rather uninteresting; a professional artist would have made a better job of many of the line diagrams. The book is amply referenced throughout for further reading, and the index is particularly strong. All in all this is

an excellent edition by a well known American surgeon, and I am sure that it will enjoy great success.

A CHIGNELL

Notes

Neuro-ophthalmology symposium

The 8th International Neuro-ophthalmology Symposium will be held at Winchester, England, on 25–29 June 1990. Details from Conference Associates, INOS, Congress House, 55 New Cavendish Street, London W1M 7RE.

Autoimmunity

The First Breton Workshop of Autoimmunity will be held on 9–10 March 1990, at the Medical School, Brest, France. Further details from Professor P Youinou, Immunologie, CHU, BP 824, F 29285, Brest Cedex, France.

Clinical vision research

The National Eye Institute will hold a course for vision researchers in Longboat Key, Florida, 25 to 28 April 1990, on 'Clinical Vision Research: epidemiologic and biostatistical approaches'. Further information from Catherine M Beinhauer, Conference Management Associates, Inc, 127 Brook Hollow, Hanover, NH 03755, USA.

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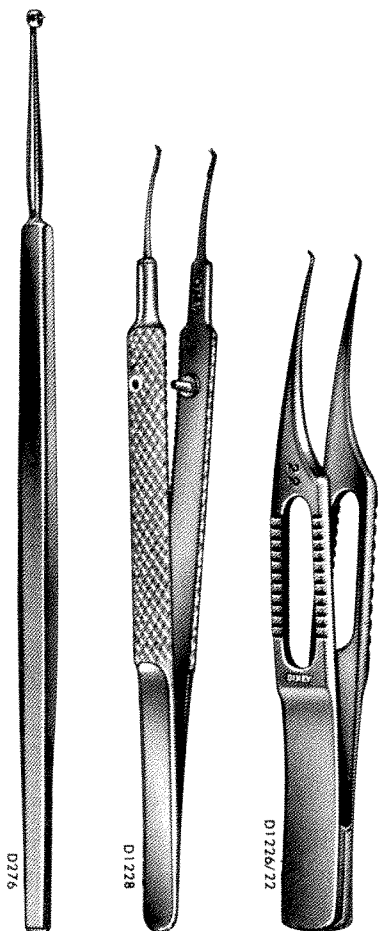
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